



CANADIAN **SMOG** SCIENCE ASSESSMENT

Volume 2: Health Effects



Health
Canada

Santé
Canada

Canada 

Health Canada is the federal department responsible for helping the people of Canada maintain and improve their health. We assess the safety of drugs and many consumer products, help improve the safety of food, and provide information to Canadians to help them make healthy decisions. We provide health services to First Nations people and to Inuit communities. We work with the provinces to ensure our health care system serves the needs of Canadians.

Également disponible en français sous le titre :

ÉVALUATION SCIENTIFIQUE CANADIENNE DU SMOG. Volume 2: Effets sur la santé

To obtain additional copies, please contact:

Publications

Health Canada

AL 0900C2

Ottawa, Ontario K1A 0K9

Tel.: 613-957-2991

Toll free: 1-866-225-0709

Fax: 613-941-5366

TTY: 1-800-267-1245 (Health Canada)

Email: publications@hc-sc.gc.ca

This publication can be made available in alternative formats upon request.

© Health Canada, 2013

Publication date: July 2013

This publication may be reproduced for personal or internal use only without permission provided the source is fully acknowledged. However, multiple copy reproduction of this publication in whole or in part for purposes of resale or redistribution requires the prior written permission from the Minister of Public Works and Government Services Canada, Ottawa, Ontario K1A 0S5 or copyright.droitdauteur@pwgsc.gc.ca.

Cat.: En88-5/2-2013E-PDF

ISBN: 978-1-100-22463-3

Pub.: 130107

Acknowledgements

This document has been prepared by the following staff of the Air Health Sciences Division of Health Canada:

- Jacques-Francois Cartier
- Guillaume Colas
- Tatiana Dinu
- Katherine Guindon-Kezis
- Barry Jessiman
- Vanessa Beaulac
- Jill Kearney
- Cheryl Khoury
- Ninon Lyrette
- Ron Newhook
- Pierre Raymond
- Jeff Willey

Parts of this draft document are based on background information prepared by the following individuals who are not employees of Health Canada:

- Mark Goldberg, McGill University (epidemiology)
- Colleen Purtill, Toxico-Logic Consulting Inc., with assistance from Rhonda Taylor (toxicology studies of ozone in animals and humans)
- Tim Ramsay, University of Ottawa (measurement error issues for PM)
- Lance Wallace, retired from US EPA (input to drafts of Exposure Assessment section for PM)
- Scott Weichenthal, McGill University (chemical composition of PM)

The health-related chapters were reviewed by the following scientific experts:

- Mark Frampton, M.D. – University of Rochester Medical Center
- Alison Geyh, Ph.D. – Johns Hopkins Bloomberg School of Public Health
- Bernard Goldstein, M.D. – University of Pittsburgh Graduate School of Public Health
- Terry Gordon, Ph.D. – New York University
- Gerard Hoek, Ph.D. – Utrecht University
- Paul Lioy, Ph. D. – University of Medicine and Dentistry of New Jersey
- Jonathan Samet, M.D. – University of Southern California
- Frank Speizer, M.D. – Harvard Medical School
- Ira Tager, M.D. – University of California, Berkeley
- John Vandenberg, Ph.D. – U.S. Environmental Protection Agency

Table of Contents

Table of Contents.....	ii
List of Abbreviations and Acronyms	x
List of Tables	xvi
List of Figures	xvii
Chapter 13: Introduction to Volume 2 of the Canadian Smog Science Assessment	1
13.1 Canadian Air Quality Policy Context	1
13.2 Brief History of Past Assessments in Canada and the US	3
13.3 Evolution of Smog Health Science	4
13.4 The Approach for Inclusion of Data in Volume 2 of the Smog Science Assessment	5
13.5 Content of the Reports.....	6
13.5.1 Volume 1: Atmospheric Science and Environmental/Economic Impacts (Chapters 2–12).....	6
13.5.2 Volume 2: Health Effects (Chapters 13–15).....	7
13.5.3 Summary Report of Highlights and Key Messages	7
13.6 References	8
Chapter 14: Health Effects of Ambient Fine Particulate Matter	9
14.1 Exposure Assessment.....	9
14.1.1 Introduction.....	9
14.1.2 Concepts in Exposure to Particulate Matter	9
14.1.3 Summary of Previous Assessments	11
14.1.3.1 Health Canada/Environment Canada 1999 PM SAD	11
14.1.3.2 US EPA 2004 PM AQCD	11
14.1.4 Recent Ambient Levels of Fine PM in Canada.....	12
14.1.5 Personal Exposure Levels	14
14.1.5.1 Overview of Methods for Determining Personal Exposure	14
14.1.5.2 Summary of Personal Exposure Studies.....	15
14.1.5.3 Canadian Studies	20
14.1.5.3.1 Toronto RTI Study (1995–1996)—general population	20
14.1.5.3.2 St. John (July–August 1995)—older adults with cardiorespiratory illness	21
14.1.5.3.3 Prince George (February–March 2001)—healthy children.....	21
14.1.5.3.4 Vancouver (April–September 1998)—non-smoking adults with COPD21	21
14.1.5.3.5 Toronto (August 1999–November 2001)—non-smoking adults with heart disease	21
14.1.5.4 US and European Studies	22
14.1.5.4.1 PM _{2.5} and PM ₁₀	22
14.1.5.4.2 PM _{10–2.5}	22
14.1.5.4.3 Continuous PM measures (personal DataRam)	22
14.1.5.4.4 Ultrafine particles	23
14.1.6 Chemical Constituents of Personal Exposure Samples	25
14.1.6.1 Elemental and Organic Carbon.....	25
14.1.6.1.1 Summary of personal exposure studies for elemental and organic carbon.....	25
14.1.6.2 Trace Elements and Ions.....	27
14.1.6.2.1 Summary of personal exposure studies for trace elements and ionic compounds	28
14.1.6.3 Polycyclic Aromatic Hydrocarbons.....	30
14.1.6.3.1 Summary of personal exposure studies for polycyclic aromatic hydrocarbons	31

14.1.7 Sources/Factors Affecting Personal Exposure to Ambient PM.....	32
14.1.7.1 Time-activity	32
14.1.7.2 Personal Exposure to Ambient PM That Has Infiltrated Indoors.....	36
14.1.7.2.1 Estimates of F_{inf} and ambient/non-ambient components of indoor levels	36
14.1.7.2.2 Estimates of F_{pex} and ambient/non-ambient components of personal exposure.....	43
14.1.7.2.3 Determinants of F_{inf} and F_{pex} and ambient components of total personal exposure.....	50
14.1.7.2.4 Relationships between ambient levels and ambient/non-ambient components of indoor and personal exposure levels.....	58
14.1.7.3 Source Apportionment of Personal Exposure Samples.....	59
14.1.8 Exposure Measurement Error Issues in PM Epidemiology.....	62
14.1.9 Summary and Considerations: Exposure Assessment.....	65
14.2 Dosimetry	69
14.2.1 Introduction.....	69
14.2.2 Types of Air Flow	69
14.2.2.1 Reynolds Flow Rate.....	69
14.2.3 Types of Particle Deposition	70
14.2.3.1 Particle Deposition in the Respiratory Tract by Particle Size.....	71
14.2.3.2 Hygroscopic Changes to Particle Size	72
14.2.4 Biological Factors Affecting Particle Deposition	73
14.2.4.1 Minute Volume, Tidal Volume and Respiratory Rate.....	73
14.2.4.2 Differences in Biological Factors.....	73
14.2.4.2.1 Gender.....	73
14.2.4.2.2 Activity patterns and physical exercise	73
14.2.4.2.3 Age	74
14.2.4.2.4 Respiratory tract disease.....	75
14.2.4.2.5 Anatomical differences in humans.....	76
14.2.5 Particle Clearance and Particle Overload	77
14.2.5.1 Mechanisms and Pathways of Clearance	77
14.2.5.2 Clearance Kinetics.....	78
14.2.5.3 Particle Overload	79
14.2.6 Modelling Deposition in the Respiratory Tract.....	80
14.2.6.1 Cast Models.....	80
14.2.6.2 Computer/Dosimetry Models	81
14.2.6.2.1 Empirical models.....	81
14.2.6.2.2 Deterministic models.....	82
14.2.7 Interspecies Variation	83
14.2.7.1 Differences in Laboratory Exposure Protocol.....	83
14.2.7.2 Anatomical and Physiological Differences between Human and Animal Lungs (with specific reference to rat anatomy)	84
14.2.7.3 PM Dosimetry in Rats versus Humans.....	85
14.2.7.4 Interspecies Model Extrapolation	85
14.2.8 Summary and Considerations: Dosimetry.....	85
14.3 Animal Toxicology	87
14.3.1 Introduction.....	87
14.3.2 Cardiovascular Effects of PM.....	87
14.3.2.1 Cardiovascular Injury, Inflammation and Atherosclerosis	88
14.3.2.2 Hemodynamic Effects and Blood Coagulability.....	90
14.3.2.3 Effects on the Vasculature	92

14.3.2.4 Direct Effects on Cardiac Function.....	94
14.3.3 Lung Injury and Inflammation.....	99
14.3.3.1 <i>In Vivo</i> Studies of Lung Injury and Inflammation	99
14.3.3.2 <i>In Vitro</i> Studies of Inflammatory Responses and Cell Damage	104
14.3.3.3 Oxidative Stress and Airway Injury and Inflammation	109
14.3.4 Experimental Allergy and PM Exposure.....	111
14.3.5 Lung Function and Airway Reactivity	116
14.3.6 Susceptibility and Compromised Animal Models.....	117
14.3.6.1 Effects of PM on Host Defence and Response to Pathogens	117
14.3.6.2 Pre-existing Disease and Susceptibility to PM	119
14.3.6.3 Other Susceptibility Factors	122
14.3.7 Particle Effects beyond the Cardiopulmonary System.....	123
14.3.7.1 Effects on the Central Nervous System	124
14.3.7.2 Developmental and Reproductive Effects	125
14.3.7.3 Effects on Other Systems	125
14.3.8 Carcinogenicity and Genotoxicity of PM.....	126
14.3.9 Exposure to Mixtures of Particles and Other Pollutants	131
14.3.10 Summary and Considerations: Animal Toxicology	133
14.4 Controlled Human Exposure Studies	139
14.4.1 Introduction.....	139
14.4.2 Review of Previous Assessments	139
14.4.3 Respiratory Effects	140
14.4.4 Effects on Biological Markers.....	141
14.4.5 Cardiovascular Effects.....	144
14.4.6 Summary and Considerations: Controlled Human Exposure Studies.....	145
14.5 Acute Exposure Epidemiological Studies.....	147
14.5.1 Mortality.....	148
14.5.1.1 Summary of Previous Assessments	148
14.5.1.2 All-Cause Mortality.....	149
14.5.1.2.1 Canadian studies	149
14.5.1.2.2 US studies.....	151
14.5.1.2.3 European studies	155
14.5.1.2.4 Australian studies.....	160
14.5.1.2.5 Other studies.....	160
14.5.1.3 Respiratory Mortality.....	161
14.5.1.3.1 Canadian studies	161
14.5.1.3.2 US studies.....	161
14.5.1.3.3 European studies	163
14.5.1.3.4 Australian studies.....	165
14.5.1.3.5 Other studies.....	165
14.5.1.4 Cardiovascular Mortality	165
14.5.1.4.1 Canadian studies	166
14.5.1.4.2 US studies.....	166
14.5.1.4.3 European studies	169
14.5.1.4.4 Australian studies.....	171
14.5.1.4.5 Other studies.....	171
14.5.1.5 Summary and Considerations: Acute Mortality	172
14.5.2 Hospital Admissions	181
14.5.2.1 Summary of Previous Assessments	181
14.5.2.2 Respiratory Admissions	182

14.5.2.2.1 Canadian studies	182
14.5.2.2.2 US studies.....	184
14.5.2.2.3 European studies	185
14.5.2.2.4 Australian studies.....	186
14.5.2.2.5 Other studies.....	188
14.5.2.3 Cardiovascular Admissions.....	188
14.5.2.3.1 Canadian studies	188
14.5.2.3.2 US studies.....	189
14.5.2.3.3 European studies	192
14.5.2.3.4 Australian studies.....	194
14.5.2.3.5 Other studies.....	194
14.5.2.4 Summary and Considerations: Hospital Admissions.....	195
14.5.3 Emergency Room Visits and Other Medical Visits	200
14.5.3.1 Summary of Previous Assessments	200
14.5.3.2 Respiratory Effects	201
14.5.3.2.1 All respiratory diseases	201
14.5.3.2.2 Asthma.....	203
14.5.3.2.3 Chronic obstructive pulmonary diseases	204
14.5.3.2.4 Pneumonia.....	205
14.5.3.3 Cardiovascular Effects.....	205
14.5.3.4 Other Medical Visits.....	207
14.5.3.5 Summary and Considerations: Emergency Room Visits and Other Medical Visits	210
14.5.4 Other Health Outcomes	211
14.5.4.1 Summary of Previous Assessments	211
14.5.4.2 Medication Use and Drug Sales.....	212
14.5.4.3 School Absenteeism.....	213
14.5.4.4 Summary and Considerations: Other Health Outcomes.....	214
14.5.5 Panel Studies	214
14.5.5.1 Summary of Previous Assessments	214
14.5.5.2 Respiratory Effects	215
14.5.5.3 Effects on Biological Markers.....	223
14.5.5.4 Cardiovascular Effects.....	227
14.5.5.5 Summary and Considerations: Panel Studies	235
14.5.6 Intervention Studies.....	238
14.5.6.1 Summary of Previous Assessments	238
14.5.6.2 Intervention Studies.....	239
14.5.6.3 Summary and Considerations: Intervention Studies.....	242
14.5.7 Source Apportionment Studies	243
14.5.7.1 Study Results	243
14.5.7.2 Summary and Considerations: Source Apportionment Studies.....	246
14.6 Epidemiology Studies of Developmental and Reproductive Endpoints	248
14.6.1 Summary of Previous Assessments	248
14.6.2 Birth Outcomes.....	248
14.6.2.1 Infant Mortality	248
14.6.2.2 Premature (Preterm) Births.....	249
14.6.2.3 Birth Weight.....	251
14.6.2.4 Small for Gestational Age and Intrauterine Growth Reduction	254
14.6.2.5 Other Birth Outcomes	254
14.6.3 Reproductive Effects.....	255

14.6.4 Summary and Considerations: Epidemiology Studies of Developmental and Reproductive Endpoints	255
14.7 Epidemiology Studies of Genetics	258
14.7.1 Summary of Previous Assessments	258
14.7.2 Summary and Considerations: Genetics.....	259
14.8 Chronic Exposure Epidemiology	260
14.8.1 Mortality Studies	260
14.8.1.1 Summary of Previous Assessments	260
14.8.1.2 Total Mortality	262
14.8.1.3 Respiratory Mortality.....	265
14.8.1.4 Cardiovascular Mortality	267
14.8.1.5 Summary and Considerations: Chronic Mortality Studies.....	270
14.8.2 Morbidity Studies	271
14.8.2.1 Summary of the 1999 PM SAD.....	271
14.8.2.2 Summary of the US EPA 2004 PM AQCD	272
14.8.2.3 Respiratory Outcomes	272
14.8.2.4 Cardiovascular Outcomes.....	279
14.8.2.5 Summary and Considerations: Chronic Morbidity Studies.....	280
14.9 Risk Characterization.....	282
14.9.1 Introduction.....	282
14.9.2 Summary of Exposure and Effects.....	282
14.9.2.1 Exposure Summary	282
14.9.2.2 Summary of Effects in Laboratory Animals	284
14.9.2.3 Summary of Effects in Controlled Human Exposure Studies.....	288
14.9.2.4 Summary of Effects in Epidemiological Studies	289
14.9.2.4.1 Acute exposure mortality.....	289
14.9.2.4.2 Hospital admissions	291
14.9.2.4.3 Emergency room and other medical visits	292
14.9.2.4.4 Panel studies	293
14.9.2.4.5 Chronic exposure mortality.....	294
14.9.2.4.6 Chronic exposure morbidity.....	295
14.9.3 Weight of Evidence for Various Categories of Effects	296
14.9.3.1 Introduction and Criteria for Causality	296
14.9.3.2 Respiratory Morbidity and Mortality Associated with Acute Exposure	297
14.9.3.2.1 Lung function	297
14.9.3.2.2 Respiratory symptoms.....	298
14.9.3.2.3 Lung injury and inflammation.....	298
14.9.3.2.4 Emergency room and other medical visits	299
14.9.3.2.5 Hospital admissions	299
14.9.3.2.6 Premature mortality	300
14.9.3.2.7 Conclusions for acute exposure respiratory effects	300
14.9.3.3 Respiratory Morbidity and Mortality Associated with Chronic Exposure.....	301
14.9.3.4 Cardiovascular Morbidity and Mortality Associated with Acute Exposure.....	302
14.9.3.4.1 Vascular function.....	302
14.9.3.4.2 Cardiac function	302
14.9.3.4.3 Emergency room visits	303
14.9.3.4.4 Hospital admissions	303
14.9.3.4.5 Premature mortality	304
14.9.3.4.6 Conclusions for acute exposure cardiovascular effects of PM.....	304
14.9.3.5 Cardiovascular Morbidity and Mortality Associated with Chronic Exposure	305

14.9.3.6 Total Mortality	305
14.9.3.7 Other Effects.....	306
14.9.3.8 Subgroups with Increased Sensitivity or Exposure.....	306
14.9.4 Shape of the Concentration–Response Curve	308
14.9.5 Uncertainties in Assessment of Health Effects of PM.....	309
14.9.6 Conclusions	312
14.10 References	317
15 Health Effects of Ground-level Ozone	380
15.1 Exposure Assessment	380
15.1.1 Ambient Ozone: Levels and Patterns.....	380
15.1.2 Indoor Environments—Levels and Determinants of Ozone.....	385
15.1.3 Personal Exposure to Ozone	390
15.1.4 Summary and Considerations: Exposure Assessment.....	396
15.2 Dosimetry	399
15.2.1 Dosimetry of Ozone in the Respiratory Tract	399
15.2.2 Species Homology and Animal-to-human Extrapolation	401
15.2.3 Summary and Considerations: Dosimetry.....	402
15.3 Animal Toxicology	403
15.3.1 Effects on the Respiratory System.....	403
15.3.1.1 Lung Injury and Inflammation.....	403
15.3.1.2 Pulmonary Function and Airway Responsiveness	407
15.3.1.3 Experimental Allergy.....	410
15.3.2 Effects on Host Defence	411
15.3.3 Systemic Effects beyond the Pulmonary System	412
15.3.3.1 Effects on the Central Nervous System	412
15.3.3.2 Cardiovascular and Other Systemic Effects.....	414
15.3.4 Susceptibility.....	416
15.3.5 Reproductive and Developmental Effects	417
15.3.6 Carcinogenicity and Genotoxicity.....	419
15.3.7 Effects of Chemical Mixtures Containing Ozone	420
15.3.8 Summary and Considerations: Animal Toxicology	422
15.4 Controlled Human Exposure Studies	426
15.4.1 Summary of Previous Assessments	426
15.4.2 Respiratory Effects	428
15.4.2.1 Acute Exposure	428
15.4.2.2 Prolonged and Repeated Exposures	429
15.4.3 Effects on Biological Markers.....	431
15.4.3.1 Acute Exposure	431
15.4.3.2 Prolonged and Repeated Exposures	433
15.4.4 Cytotoxicity, Genotoxicity and Other Effects	434
15.4.5 Summary and Considerations: Controlled Human Exposure Studies.....	435
15.5 Acute Exposure Epidemiology	438
15.5.1 Mortality	439
15.5.1.1 Summary of Previous Assessments	439
15.5.1.2 Mortality Studies	439
15.5.1.3 Summary and Considerations: Acute Mortality	442
15.5.2 Hospital Admissions	447
15.5.2.1 Summary of Previous Assessments	447
15.5.2.2 Respiratory Admissions	447
15.5.2.3 Cardiovascular Admissions.....	449

15.5.2.4 Summary and Considerations: Hospital Admissions	449
15.5.3 Emergency Room Visits and Other Health Outcomes.....	453
15.5.3.1 Summary of Previous Assessments	453
15.5.3.2 Respiratory Emergency Room Visits	453
15.5.3.3 Cardiovascular Emergency Room Visits	454
15.5.3.4 Other Health Outcomes (Physician Visits, Disability Days, School Absenteeism)	454
15.5.3.5 Summary and Considerations: Emergency Room Visits and Other Health Outcomes.....	455
15.5.4 Panel Studies	456
15.5.4.1 Summary of Previous Assessments	456
15.5.4.2 Respiratory Effects	456
15.5.4.3 Effects on Biological Markers.....	458
15.5.4.4 Cardiovascular Effects	459
15.5.4.5 Summary and Considerations: Panel Studies	460
15.6 Epidemiology Studies of Developmental and Reproductive Endpoints	462
15.6.1 Summary of Previous Assessments	462
15.6.2 Birth Outcome Endpoints.....	462
15.6.2.1 Infant Mortality	462
15.6.2.2 Birth Weight.....	462
15.6.2.3 Small for Gestational Age and Intrauterine Growth Reduction	464
15.6.2.4 Premature (Preterm) Births.....	464
15.6.2.5 Other Birth Outcomes	465
15.6.3 Reproductive Studies.....	466
15.6.4 Summary and Considerations: Epidemiology Studies of Developmental and Reproductive Endpoints	466
15.7 Epidemiology Studies of Genetics	468
15.7.1 Summary of Previous Assessments	468
15.7.2 Genetic Susceptibility	468
15.7.3 Genotoxicity.....	469
15.7.4 Summary and Considerations: Epidemiology Studies of Genetics	470
15.8 Chronic Exposure Epidemiology	471
15.8.1 Summary of Previous Assessments	471
15.8.2 Mortality.....	471
15.8.3 Diabetes	471
15.8.4 Summary and Considerations: Chronic Exposure Epidemiology	472
15.9 Risk Characterization.....	474
15.9.1 Introduction.....	474
15.9.2 Summary of Exposure and Effects.....	474
15.9.2.1 Summary of Exposure	474
15.9.2.2 Summary of Effects in Laboratory Animals	476
15.9.2.3 Summary of Effects in Controlled Human Exposure Studies.....	478
15.9.2.4 Summary of Effects in Epidemiological Studies	479
15.9.2.4.1 Acute mortality	479
15.9.2.4.2 Hospital admissions	480
15.9.2.4.3 Emergency room visits	481
15.9.2.4.4 Panel studies	482
15.9.2.4.5 Effects of chronic exposure	482
15.9.2.4.6 Developmental and reproductive effects.....	483
15.9.3 Weight of Evidence for Various Categories of Effects.....	484
15.9.3.1 Introduction and Criteria for Causality	484

15.9.3.2 Respiratory Morbidity Associated with Acute Exposure	485
15.9.3.2.1 Lung function	485
15.9.3.2.2 Respiratory symptoms.....	485
15.9.3.2.3 Lung injury and inflammation.....	485
15.9.3.2.4 Airway hyperresponsiveness.....	486
15.9.3.2.5 Hospital admissions and emergency room visits	486
15.9.3.2.6 Conclusion for respiratory morbidity	486
15.9.3.3 Cardiovascular Morbidity Associated with Acute Exposure	487
15.9.3.4 Mortality Associated with Acute Exposure	488
15.9.3.5 Effects Associated with Chronic Exposure.....	488
15.9.3.6 Subgroups with Increased Sensitivity or Exposure to Ambient Ozone	489
15.9.4 Shape of the Concentration–Response Curve	490
15.9.5 Uncertainties in Assessment of Health Effects of Ozone	491
15.9.6 Conclusions	494
15.10 References	497

List of Abbreviations and Acronyms

1-NN	1-nitronaphthalene
5-HIAA	5-hydroxyindolacetic acid
8-oxodG	7-hydro-8-oxo-2'-deoxyguanosine
ABS	absorbance
A/C	air conditioning system
ACh	acetylcholine
ACS	American Cancer Society
AEC	alveolar epithelial cell
AED	aerodynamic equivalent diameter
AER	air exchange rate
AGA	average for gestational age
AHR	airway hyperresponsiveness
AHSMOG	Adventist Health Study on the Health Effects of Smog
AIRS	(US EPA) Area Information Records System
Al	aluminum
AM	alveolar macrophage
AMP	accumulation mode particle
AN	arcuate nucleus
APHEA	Air Pollution and Health: a European Approach (project)
ApoE ^{-/-}	apolipoprotein E-deficient (mice)
AQBAT	Air Quality Benefits Assessment Tool
AQCD	Air Quality Criteria Document
ARIC	Atherosclerosis Risk in Communities (study)
ARIES	Aerosol Research and Inhalation Epidemiology Study
As	arsenic
BAL	bronchoalveolar lavage
BALF	bronchoalveolar lavage fluid
BC	black carbon
Be	beryllium
BFx	bronchial fraction of BAL fluid
BHR	bronchial hyperreactivity
BMI	body mass index
bpm	beats per minute
Br	bromine
BS	black smoke
bsp	light-scattering coefficient
BW	bronchial wash
C	carbon
C3	complement factor 3
Ca	calcium
Cal/EPA	California Environmental Protection Agency
CAMP	Childhood Asthma Management Program
CAP	concentrated ambient particle
CAPMoN	Canadian Air and Precipitation Monitoring Network
CAR	centriacinar region
CB	carbon black
CC16	Clara cell protein
CCL	C-C motif ligand

CCME	Canadian Council of Ministers of the Environment
CCR	C-C motif receptor
Cd	cadmium
Ce	cerium
CEPA	Canadian Environmental Protection Act
CFD	computational fluid dynamics
CFPD	computational fluid-particle dynamics
CHD	coronary heart disease
CHF	congestive heart failure
CHS	Children's Health Study (in Southern California)
CI	confidence interval
CIMT	carotid intimal medial thickness
CMD	count median diameter
CNS	central nervous system
CO	carbon monoxide
Co	cobalt
COH	coefficient of haze
COPD	chronic obstructive pulmonary disease
COX	cyclooxygenase
Cr	chromium
CRP	C-reactive protein
Cu	copper
CVD	cardiovascular disease
CWS	Canada-Wide Standards
CXCL	C-X-C motif ligand
d	day
DEP	diesel exhaust particle
DK	double knockout (mice)
DMTU	dimethylthiourea
DNA	deoxyribonucleic acid
DTPA	diethylenetriamine penta-acetic acid
DWTD	distance-weighted traffic density
EC	elemental carbon
ECG	electrocardiogram
EGFR	epidermal growth factor receptor
EIB	exercise-induced bronchitis
ELF	epithelial lining fluid
eNOS	endothelial nitric oxide synthase
EPA	Environmental Protection Agency
EPIC	European Prospective Investigation into Cancer and Nutrition (study)
ERK	extracellular signal-regulated kinase
ERV	emergency room visit
ESR	electron spin resonance
ET	extrathoracic
ET-1	endothelin-1
ETS	environmental tobacco smoke
Fe	iron
FEF ₂₅₋₇₅	maximum mid-expiratory flow
FEF ₇₅	forced expiratory flow after 75% of expired volume
FeNO	fraction of exhaled nitric oxide
FEV ₁	forced expiratory volume in one second

Fpg	formamidopyrimidine glycosylase
FRC	functional residual capacity
FRM	Federal Reference Method
FVC	forced vital capacity
FVII	factor VII
GAM	generalized additive model
GC	gas chromatography
GBP	granular bio-durable particle
GEE	generalized estimating equation
GIS	Geographic Information System
GLM	generalized linear model
GM	geometric mean
GM-CSF	granulocyte-macrophage colony-stimulating factor
GPx	glutathione peroxidase
GRx	glutathione reductase
GSH	glutathione
GST	glutathione-S-transferase
GSTM1	glutathione-s-transferase mu 1
GSTP1	glutathione-s-transferase pi 1
h	hour
H+	hydron
H ₂ O ₂	hydrogen peroxide
H ₂ SO ₄	sulphuric acid
HAPC	Harvard Ambient Particle Concentrator
HDMA	house dust mite allergen
HDR	hospital discharge register
HEPA	high-efficiency particulate air
HF	high frequency
HFE	hemochromatosis gene
HFnu	HF/[HF+LF]
HO-1	heme oxygenase-1
HPLC	high-performance liquid chromatography
HR	heart rate
HRV	heart rate variability
HVAC	heating, ventilating and air conditioning
ICAM-1	inter-cellular adhesion molecule 1
ICD	implantable cardioverter-defibrillator
ICRP	International Commission on Radiological Protection
IFN	interferon
IgE	immunoglobulin E
IHD	ischemic heart disease
IL	interleukin
Ile	isoleucine
iNOS	inducible nitric oxide synthase
I/O	indoor/outdoor
IQR	interquartile range
Ir	iridium
ISAAC	International Study of Asthma and Allergy in Childhood
IUGR	intrauterine growth retardation
K	potassium
L/W	lumen/wall (area)

La	lanthanum
LBW	low birth weight
LDH	lactate dehydrogenase
LF	low frequency
LF:HF	low frequency to high frequency ratio
Li	lithium
LO	lipoxygenase
LOD	limit of detection
LOESS	locally weighted scatterplot smoothing
LPS	lipopolysaccharide
LRD	lower respiratory disease
LRT	long-range transport
LRTI	lower respiratory tract infection
LTA	lipoteichoic acid
LTE4	leukotriene E4 (eicosanoid lipid mediator)
LVDP	left ventricular developing pressure
MAPK	mitogen-activated protein kinase
MCh	methacholine
MCL	mean cycle length of R-R intervals for normal heartbeats
MCM	mucous cell metaplasia
MCP	monocyte chemoattractant protein
MCT	monocrotaline
MDA	malondialdehyde
MEF	mean expiratory flow
MESA	Multi-ethnic Study of Atherosclerosis
Mg	magnesium
MI	myocardial infarction
min	minute
MIP	macrophage inflammatory protein
MMAD	mass median aerodynamic diameter
MMEF	maximal mid-expiratory flow rate
MMP	matrix metalloproteinase
MMT	methylcyclopentadienyl manganese tricarbonyl
Mn	manganese
MNC	mononuclear cell
MPA	medial preoptic area
MPO	myeloperoxidase
MPPD	multipath particle dosimetry model
mRNA	messenger ribonucleic acid
NAC	N-acetylcysteine
NADPH	nicotinamide adenine dinucleotide phosphate-oxidase
NAPS	National Air Pollution Surveillance
NC	number concentration
ND	non-detectable
NF- κ B	nuclear factor kappa B
NGF	nerve growth factor
NH ₃	ammonia
NH ₄	ammonium
NH ₄ HSO ₄	ammonium bisulphate
NHBE	normal human bronchial epithelial
Ni	nickel

NMD	number median diameter
NMHC	non-methane hydrocarbons
NMMAPS	National Morbidity and Mortality Air Pollution Study
NMP	nucleation mode particle
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
NO ₂	nitrogen dioxide
NO ₃	nitrate
NOS	nitric oxide synthase
NO _x	nitrogen oxide
NYU	New York University
O ₃	ozone
OC	organic carbon
OH-	hydroxide anion
·OH-	hydroxyl radical
OHC	oxygenated hydrocarbon
OR	odds ratio
OVA	ovalbumin
PAH	polycyclic aromatic hydrocarbon
Pb	lead
pDR	personal DataRAM
PE	pulmonary exacerbation
PEFR	peak expiratory flow rate
PEM	personal exposure monitor
Penh	enhanced pause
PI	posterior interval
PM	particulate matter
PM ₁₀	particulate matter of 10 µm or less in diameter
PM _{10-2.5}	coarse particulate matter, with a diameter between 2.5 and 10 µm
PM _{2.5}	fine particulate matter, with a diameter of 2.5 µm or less
PMN	polymorphonuclear leukocyte
PN	particle number
PNC	particle number concentration
PNN50	time domain measure of heart rate variability
ppm	parts per million
Pt	platinum
Qtc	Q-T corrected
R	Spearman correlation coefficient
RAIAP	Respiratory Allergy and Inflammation due to Ambient Particles
R _{aw}	lung function–airway resistance
RAW 264.7	mouse leukaemic monocyte macrophage cell line
RBC	red blood cell
Re	Reynolds number
REM	rapid eye movement
RMSSD	mean squared differences of successive RR intervals
RNA	ribonucleic acid
RNS	reactive nitrogen species
RO	residual oil
ROFA	residual oil fly ash
ROS	reactive oxygen species
RR	relative risk

R-R interval	inter-beat (heart) interval
RS	resuspended soil
RSV	respiratory syncytial virus
RT	respiratory tract
RTLFL	respiratory tract lining fluid
S	sulphur
SAA	serum amyloid A
SAD	Science Assessment Document
SCARPOL	Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen
SD	standard deviation
SDANN	standard deviation of average N-N intervals within successive 5-min blocks
SDNN	standard deviation of normal to normal beat intervals
Se	selenium
SE	standard error
SES	socioeconomic status
SGA	small for gestational age
SH	spontaneously hypertensive
Si	silicon
SIDS	Sudden Infant Death Syndrome
SiO ₂	silicone dioxide
Sm	samarium
Sn	tin
SO ₂	sulphur dioxide
SO ₃	sulphur trioxide
SO ₄ ²⁻	sulphate
SOD	superoxide dismutase
SP	surfactant protein
SPM	suspended particulate matter
SpO ₂	arterial oxygen saturation as determined by pulse oximetry
SPT	skin prick test
SR	scavenger receptor
Sr	strontium
SRM	standard reference material
SS	secondary sulphate
SVE	supraventricular ectopy (extra heartbeats)
TB	tracheobronchial
TBARS	thiobarbituric acid-reactive substances
TDF	total respiratory tract deposition fraction
TEOM	tapered element oscillating microbalance
TGF	transforming growth factor
Ti	titanium
TiO ₂	titanium dioxide
TLC	total lung capacity
TLR	Toll-like receptor
TNF	tumour necrosis factor
TOS	time of onset of symptoms
TRII	triangular index
TSP	Total suspended particles
UFP	ultrafine particle

ULTRA	Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (study)
URD	upper respiratory disease
URTI	upper respiratory tract infection
US EPA	United States Environmental Protection Agency
V	vanadium
vCAM	vascular cell adhesion molecule
VLBW	very low birth weight
VOC	volatile organic compound
VOSO ₄	vanadyl sulphate
VPB	ventricular premature beat
V _t	tidal volume
vWF	von Willebrand factor
WBC	white blood cells
WKY	Wistar-Kyoto rat strain
Zn	zinc
Δψ _m	mitochondrial membrane potential change

List of Tables

Chapter 14

Table 14.1	Results from the Canadian Human Activity Pattern Study
Table 14.2	Mean air exchange rate (AER), F _{inf} and outdoor contribution to personal exposure, by season (Raleigh, NC, panel study) (Source: Wallace et al., 2006b)
Table 14.3	Source apportionment studies
Table 14.4	Anatomical parameters, and clearance and ventilatory values for humans and rats used in the dosimetry model calculations (Source: Brown et al., 2005)
Table 14.5	Qualitative summary of particle effects on the cardiovascular system in animal toxicology studies
Table 14.6	Qualitative summary of susceptibility studies using compromised animal models
Table 14.7	Qualitative summary of particle effects beyond the cardiopulmonary system in animal toxicology studies

Chapter 15

Table 15.1	US and Canadian studies of ozone levels (ppb) and determinants in indoor environments (modified from US EPA, 2006)
Table 15.2	US and Canadian studies of levels (in ppb) and determinants of personal exposure to ozone (modified from US EPA, 2006)
Table 15.3	Qualitative summary of ozone health effects in reviewed animal toxicology studies

List of Figures

Chapter 14

- Figure 14.1 PM exposure framework
- Figure 14.2. Spatial distribution of the 98th percentile 24-h PM_{2.5} concentrations ($\mu\text{g}/\text{m}^3$) across Canada and the US for 2004–2006
- Figure 14.3 Personal, indoor, outdoor and ambient PM_{2.5} levels from various studies (medians or geometric means)
- Figure 14.4 Personal, indoor, outdoor and ambient PM₁₀ levels from various studies (medians or geometric means)
- Figure 14.5. Mean residential PM_{2.5} F_{inf} from various studies
- Figure 14.6. Mean ambient and non-ambient components of indoor PM_{2.5} from various studies
- Figure 14.7 Mean PM_{2.5} personal exposure factor (F_{pex}) from various studies
- Figure 14.8 Mean ambient and non-ambient source contributions to total PM_{2.5} personal exposure
- Figure 14.9a Total PM_{2.5} personal exposure vs. ambient PM_{2.5} for 16 COPD subjects in Vancouver (Source: Wilson and Brauer, 2006)
- Figure 14.9b Ambient component of PM_{2.5} personal exposure vs. ambient PM_{2.5} for 16 COPD subjects in Vancouver (Source: Wilson and Brauer, 2006)
- Figure 14.9c Non-ambient component of PM_{2.5} personal exposure vs. ambient PM_{2.5} for 16 COPD subjects in Vancouver (Source: Wilson and Brauer, 2006)
- Figure 14.10 The respiratory tract (from Wang, 2005)
- Figure 14.11 Deposition fraction for total results of LUDEP model for an adult male worker (ICRP default breathing parameters) showing total percentage of deposition in the respiratory tracts (TOT) and in the ET, TB, and alveolar (A) regions: (a) nasal breathing (NB), (b) mouth breathing (MB), (c) comparison of nasal and mouth breathing for TB and A regions (from US EPA, 2004).
- Figure 14.12 Potential pathophysiological mechanisms for the effects of air pollutants on the cardiovascular system (Adapted from Routledge and Ayres, 2005)
- Figure 14.13 Risk estimates for total mortality per 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ concentration in single-pollutant models
- Figure 14.14 Risk estimates for total mortality per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration in single-pollutant models
- Figure 14.15 Risk estimates for total mortality per 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ concentration in single-pollutant models
- Figure 14.16 Risk estimates for respiratory mortality per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration in single-pollutant models
- Figure 14.17 Risk estimates for cardiovascular mortality per 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ concentration in single-pollutant models
- Figure 14.18 Risk estimates for cardiovascular mortality per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} concentration in single-pollutant models

- Figure 14.19 Risk estimates for respiratory hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} concentration in single-pollutant models
- Figure 14.20 Risk estimates for cardiovascular hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} concentration in single-pollutant models
- Figure 14.21 Risk estimates for respiratory hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration in single-pollutant models
- Figure 14.22 Risk estimates for cardiovascular hospitalization per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration in single-pollutant models

Chapter 15

- Figure 15.1 Spatial distribution of the 3-year-average fourth highest daily maximum 8-h ozone concentration in ppb (2004–2006)
- Figure 15.2 Mean (\square) and mean daily maximum (\square) ozone (ppb) by month averaged for the years 2001 to 2005 (Note: mean ozone concentration in ppb shown on y-axis)
- Figure 15.3 Diurnal variations in ozone concentration (ppb)—summer (May–Sep) (\square) and winter (Nov–Mar) (\square) averaged for years 2001 to 2005 (Note: Mean ozone concentration in ppb shown on y-axis)
- Figure 15.4 Diurnal variations in ozone concentration (ppb)—weekday (\square) and weekend (\square) for summertime (May–September) averaged for years 2001 to 2005 (Note: mean ozone concentration in ppb shown on y-axis)
- Figure 15.5 Risk estimates for total mortality per 10-ppb increase in 8-h ozone/6.7 ppb increase in 24-h ozone concentration in single-pollutant models
- Figure 15.6 Risk estimates for respiratory mortality per 10-ppb increase in 8-h ozone/13.3-ppb increase in 1-h ozone concentration in single-pollutant models
- Figure 15.7 Risk estimates for cardiovascular mortality per 10-ppb increase in 8-h ozone/6.7-ppb increase in 24-h ozone concentration in single-pollutant models
- Figure 15.8 Risk estimates for respiratory hospitalization per 10-ppb increase in 8-h ozone/13.3-ppb increase in 1-h ozone concentration in single-pollutant models
- Figure 15.9 Risk estimates for cardiovascular hospitalization per 10-ppb increase in 8-h ozone concentration in single-pollutant models

Chapter 13: Introduction to Volume 2 of the Canadian Smog Science Assessment

The Canadian Smog Science Assessment is a comprehensive review of the state of smog science in Canada, considering the atmospheric, human health and ecosystem health perspectives in the two volumes. The review was initiated in 2005 in response to a rapidly evolving scientific body of knowledge and was designed to feed into the next round of decision-making as Canada moves forward in the evolution of its air quality policies.

This Assessment addresses the science of particulate matter (PM) and ground-level ozone within one document. These pollutants are generally considered to be the main ingredients in “smog,” a mixture that has a significant negative impact on both human and ecosystem health. The decision to combine both PM and ozone to the degree possible in this Assessment is in response to an evolution in thinking, both in the scientific and policy communities, where the atmosphere can be considered as a single entity composed of a complex mixture of pollutants that are intricately linked. Future iterations using this approach will likely continue with a focus on these substances but may add other major air pollutants as our understanding of linkages and effects evolves.

The primary objective of this Assessment is to provide a scientific synthesis of available information on PM and ozone in Canada, in order to:

- describe the impacts of smog on ecosystems and human health;
- describe the relevance of recent scientific research on smog within the context of the Canadian policy framework;
- identify gaps and areas for further research on particulate matter and ozone; and
- determine if emission reductions aimed at targeting smog have had or will have beneficial impacts on smog levels in Canada as well as on ecosystem and human health.

Within the environmental portions of this Assessment, consideration is given to ground-level ozone, fine and coarse particulate matter (PM_{2.5} and PM_{10-2.5}), and the precursor gases that lead to the formation of these pollutants. Where needed, consideration is also given to the constituents of PM in order to understand its atmospheric and environmental sources, fate and behaviour, and its health effects. The health-related portions of this Assessment focus on ground-level ozone and fine particulate matter. Coarse particulate matter health effects are included when a specific study addresses this size in comparison to the fine fraction, but a more thorough assessment of the health effects of coarse PM is being prepared separately.

This chapter provides the context for the development of this comprehensive review, as well as a description of the process behind it and how the content is organized.

13.1 Canadian Air Quality Policy Context

Ambient air quality management in Canada is a shared responsibility among provincial, territorial, federal, international and in some cases municipal governments, made possible through an array of commitments and initiatives that have evolved over many decades.

Governments at various levels in Canada can assess air pollutants and control their impacts through the setting of ambient air quality objectives or standards. These are benchmark levels representing goals for outdoor air quality that protect public health, the environment, or aesthetic properties of the environment. They are primarily effects-based but also reflective of technological, economic and societal information. Although provincial governments have the primary responsibility for many aspects of air pollution control, federal actions are integrated with those of the other levels of government. Ambient air quality objectives or standards guide federal, provincial, territorial and regional governments in making risk management decisions and can play an important role in air quality.

Federal, provincial and territorial governments work together in partnership under the framework of the Canadian Council of Ministers of the Environment (CCME) through the 1998 Canada-wide Accord on Environmental Harmonization and the Canada-wide Standards (CWSs) Sub Agreement. Canada-wide Standards for PM_{2.5} and ozone were established in June 2000 in order to establish a comprehensive risk management strategy for these pollutants, and to minimize the risk associated with these pollutants to human health and the environment, by 2010. The PM_{2.5} and ozone CWSs were based on Science Assessment Documents published by Health Canada and Environment Canada in 1999 for these two substances (Health Canada and Environment Canada, 1999a, 1999b). These targets were based on the scientific understanding of the issue at the time and represented a balance between the desire to achieve the best health and environmental protection possible in the relative near-term and the feasibility and costs of reducing the pollutant emissions that contribute to elevated levels of PM and ozone in ambient air. The target selected for PM_{2.5} was 30 µg m⁻³ (24-h average), to be achieved by 2010 based on the 98th percentile annual value averaged over three consecutive years. The target selected for O₃ was 65 ppb (8-hour average), to be achieved by 2010 based on the fourth highest annual value averaged over three consecutive years.

Recently, governments along with a variety of stakeholders decided to institute a new approach to the setting of air quality standards and the overall management of air quality. This approach, termed the Air Quality Management System (AQMS) is in the process of developing Canadian Ambient Air Quality Standards (CAAQS), a series of industrial emission regulations (Base Line Industrial Emission Requirements or BLIERS), and a “place-based” management system for local and regional air quality. It is expected that the current assessment will assist risk managers as they implement some of the features of the AQMS.

The *Canadian Environmental Protection Act* (CEPA) provides the federal government with broad authority to address emissions into the atmosphere of substances that have negative impacts on the health and environment throughout their life cycle. CEPA was first promulgated in 1988, and was revised and renewed as a new Act in 1999 after a five-year review process. The focus of CEPA (1999) is pollution prevention and the protection of the environment and human health as a means to promote sustainable development. The Departments of Environment and Health share responsibility under CEPA to assess and manage the threats that pollutants may pose; Health Canada focuses on risks to human health, while Environment Canada focuses on risks to the environment. Ground-level ozone, PM₁₀ and gaseous precursors (sulphur dioxide, nitrogen oxides, ammonia and VOCs) have all been declared “toxic” under CEPA, meaning that they are “entering or may enter the environment in a quantity or concentration or under conditions that: have or may have an immediate long-term harmful effect on the environment or its biological diversity” (CEPA s64(a)) and “constitute or may constitute a danger in Canada to human life or health” (CEPA s64(c)).

Internationally, Canada is a signatory to the 1999 *Gothenburg Protocol to Abate Acidification, Eutrophication and Ground-level Ozone* (under the Convention on Long-Range Transport of Air Pollution) and the *Canada-U.S. Air Quality Agreement*, both of which contain measures for the

reduction of smog precursors. Canada continues to actively participate in the development of additional measures under these international agreements, including the exploration of a possible annex to the Canada-U.S. Agreement to specifically address PM.

One of the most significant influences on air quality in Canada is the United States. The two countries are in such close proximity that measures to reduce emissions in the United States will likely have a positive impact on parts of Canada.

The information and conclusions from this Assessment are primarily intended to provide scientific guidance to decision-makers in the review and/or development of air quality policies, including ambient air quality objectives and standards designed to risk manage PM and ozone in order to reduce the risk of these pollutants to the health of Canadians and their environment. The information will also provide context for international negotiations targeted to further reducing the transboundary and transcontinental flow of air pollutants. The knowledge gaps identified in this Assessment are intended to provide direction for future scientific research so that Canadian information improves to better support future policy requirements.

13.2 Brief History of Past Assessments in Canada and the US

The health and environmental effects of ambient PM and ozone have been recognized since the mid-1900s, and have previously been the subject of extensive assessments in Canada and the US, as well as other countries and organizations around the world. In 1999, Health Canada and Environment Canada completed science assessment documents (SADs) containing a detailed review and critical analysis of information about the effects of PM and ozone on human health, animals, vegetation and materials, drawing on studies published up to 1997 (Health Canada and Environment Canada, 1999a, 1999b). Several years later, the US Environmental Protection Agency (EPA) published updated air quality criteria documents (AQCD) for their 1990s-era assessments. The Air Quality Criteria for Particulate Matter (US EPA, 2004) was a multi-volume review and assessment of the evidence for health and environmental effects from exposure to ambient PM, and was followed in 2006 with an extensive assessment of ozone: Air Quality Criteria for Ozone and Related Photochemical Oxidants (US EPA, 2006).¹

The findings presented in the above peer-reviewed reports and in more recent ones focused on the atmospheric aspect of PM—including the 2001 Precursors to Ambient PM_{2.5} Assessment (Environment Canada, 2001) and the 2004 Canada-U.S. Transboundary PM Science Assessment (Canada-U.S., 2004), which emphasized the need for reductions in emissions of precursor pollutants as well as primary PM in order to achieve emission targets and to meet the Canada-wide Standards for PM and ozone. The 2004 Canada-U.S. Transboundary PM Science Assessment also demonstrated the transport of PM and its precursors across jurisdictional boundaries, highlighting the need for a multi-jurisdictional approach to air quality management.

The above documents also provided extensive evidence of a wide range of air-pollution-related effects on the environment and human health, such as increases in cardiac and/or pulmonary mortality, hospital admissions, and emergency department visits. In addition, they pointed out significant areas of uncertainty in the science and highlighted the need for continued evaluation of the atmospheric, environmental and health science in order to provide the most relevant basis for risk management strategies.

¹ The US EPA has since conducted additional analyses and reports, most notably Integrated Science Assessment reports for Particulate Matter and for Ozone. These documents were completed and available outside of the review period for this assessment.

13.3 Evolution of Smog Health Science

The relationship between air pollution and adverse health effects has been known since the mid 1900's. Over the last 60 years, much scientific inquiry has occurred into the effects of air pollution and human health. The 1999 Science Assessment Documents (SADs) for Particulate Matter and Ground-level Ozone were the first comprehensive treatments of the subject in Canada (Health Canada and Environment Canada, 1999a, 1999b). The health chapters of these documents were based upon a relatively large body of epidemiological and experimental evidence for the adverse effects of exposures to both PM and Ozone, and included a range of adverse endpoints up to and including premature death. More recent assessments continue to highlight the importance of epidemiological relationships but also highlight a series of advances in our understanding of the mechanisms and impacts of air pollution on human health. The following paragraphs summarize what we knew then and some of the scientific developments that have happened over the last decade.

The SAD for PM noted a relative lack of mechanistic and toxicological evidence to provide support for the epidemiological findings on which conclusions in that document were based. Despite this lack, the SAD concluded that the volume, quality, coherence and consistency of the epidemiologic findings were sufficient to support significant risk management actions to reduce PM_{2.5}. Since that time, an enormous new and complex database on toxicological outcomes (in human, animal and other experimental settings) has emerged that provides a mechanistic basis for the outcomes seen in epidemiologic studies. These studies also indicate the potential for PM to reach beyond the respiratory and cardiovascular systems to exert effects and preliminary findings of interactions with the Central Nervous System and reproductive systems are coming to light. However, the overall database provides clear indications that the predominant effect of PM is on the cardiovascular system. The SAD noted that chronic exposure mortality appeared to be the outcome of most importance from a public health perspective, but noted the reliance on a small number of datasets (especially the American Cancer Society (ACS) and Harvard Six Cities cohorts). While new cohorts have become available and buttress the previous findings, the most important contributions have resulted from reanalysis and extension of the ACS and Six Cities work. Findings support the original analyses but demonstrate specific impact on large susceptible subgroups (e.g. COPD patients), the dominance of PM metrics (versus gaseous) in the effects, and the ability to account for and discount a large number of potential confounders in the associations seen.

The original SAD for ozone found a relative wealth of evidence from epidemiological and experimental studies of acute exposure effects up to and including premature mortality. Since that time, research has provided additional support for these findings. Areas of concern identified in the SAD included uncertainty in exposure from the use of fixed ambient monitors for epidemiological findings (for both ozone and PM), the potential confounding effects of temperature, the importance of spirometric endpoints to denote adverse outcomes, and only weak indications of chronic-exposure effects. Recent work in the use of various modeling approaches indicates that the temperature effect on adverse outcomes is adequately addressed in epidemiological studies. Considerable new work indicates that the effect of ozone on spirometric outcomes (i.e. lung function) is separate from inflammation and airway hyperreactivity and each should be treated as relatively independent adverse outcomes. Work on the effect of chronic exposure to ozone (and other pollutants) benefited greatly from the California Children's Health Study and clearly suggests independent effects of ozone on some adverse outcomes.

For both PM_{2.5} and ozone, significant new work has provided a more robust basis for the use of ambient fixed site monitors to provide exposure indices in epidemiology studies. Work on particle components and metrics such as particle number and the ultrafine component of PM has been extensive, but to date has not provided a more specific scope for risk management

13.4 The Approach for Inclusion of Data in Volume 2 of the Smog Science Assessment

The following report does not examine the entire health-related literature for these pollutants, but instead builds on and updates the previous SAD and AQCD assessments. Hence, most subject area sections initially summarize the findings of these earlier assessments for the pollutant in question, and then critically review original papers that have been published subsequent to the relevant AQCD. For fine PM, the report primarily references studies that were published from April 2002 to the end of 2006, whereas for ozone the evaluation period runs from the beginning of 2005 to the end of 2006. Studies that were published in this time frame but were included in the AQCDs have generally not been discussed individually, though a small number of key studies are highlighted. Studies published in 2007 but prepublished online in 2006 have also been included.

The individual papers identified for the update periods were initially critiqued for study design, methodology and analytical technique before inclusion, and those deemed most relevant are reviewed in more detail. In general, more weight has been given to studies where the exposure was expected to be relevant to ambient exposures in Canada in terms of composition, sources, levels and environmental conditions. For example, more detail is presented for Canadian studies, where available, as well as data from the US and Europe. Studies from semi-tropical and tropical countries are discussed in less detail, because of differences in climate, building types, time-activity patterns, socioeconomic factors, etc., that are expected to make the findings less relevant. Similarly, less emphasis has been placed on toxicological studies that use less relevant PM types (e.g. artificial particles such as titanium dioxide (TiO₂)). More attention has been focused on studies that shed new light on the health effects of these pollutants, and less on those that have essentially repeated previous studies, although the latter are also important for validating previous findings and strengthening the evidence base.

The sections dealing with PM present information on various size-specific classes of particles. Most available studies have characterized PM as either PM₁₀ (referring to particles with an upper 50% cutpoint of 10 µm aerodynamic diameter), or its fine fraction PM_{2.5} (with an upper 50% cutpoint of 2.5 µm). However, some studies have investigated other size-specific metrics for PM, including black smoke (BS), a measure of particle reflectance previously approximated to PM₁₀ but now often equated with measurement of elemental carbon (EC), sulphate (SO₄²⁻), and increasingly, ultrafine particles (UFPs). All these PM metrics have been used in investigations of the health effects associated with particulate air pollution, and are considered to contribute to the weight of evidence for these effects. The 10 and 2.5 µm measurements are the basis of almost all air quality objectives and standards around the world, including Canada. While the purpose of this document is to lend support for the update and potential revision of the existing standards, there is the additional intent to determine if other PM metrics provide additional perspectives of interest, and to examine whether other PM metrics might provide better information for the setting of standards and the development of subsequent risk management strategies.

A growing number of studies have investigated the health effects of PM_{10-2.5}, the coarse fraction of PM₁₀. However, the findings of these studies, while they are touched on, are not discussed in

any detail in this report, which is instead focused on metrics that contain finer size fractions in order to update the existing standard. The evidence for health effects of the coarse fraction of PM₁₀ is the subject of a separate assessment currently being conducted by Health Canada.

13.5 Content of the Reports

The Canadian Smog Science Assessment consists of two volumes, as well as a published summary document that presents highlights and key findings of the Assessment.

The Assessment is intended as a document that reviews, evaluates and places in context the scientific perspectives on smog. In turn, it is expected that the document will also serve to inform subsequent policy development on national, regional and local scales. In this light, a summary of key results has been prepared from this document that highlights for policy makers and interested parties issues of particular relevance from both scientific and practical points of view. Risk managers, stakeholders and other interested parties should be able to reference specific aspects of both the summary and full assessment documents in developing policies and measures.

Volume 1 (Environment Canada, 2011) presents the state of the science on the environmental (atmospheric and ecosystem impacts) and socioeconomic aspects of PM and ozone. Volume 2 (this volume) (Health Canada, 2011) reviews the information related to the impacts of these pollutants on human health.

13.5.1 Volume 1: Atmospheric Science and Environmental/Economic Impacts (Chapters 2–12)

The chapters in Volume 1 were prepared by Environment Canada in collaboration with several academic and provincial partners. Many of its chapters cover the recent literature for the period 2003–2007 (and beyond in special cases) and some report on results of new analyses carried out specifically for this Assessment or in support of recent policy requirements.

Chapter 2 describes the physical and chemical mechanisms behind smog production, transformation, and removal from the atmosphere, as well as how these are influenced by meteorology. Chapter 3 focuses on monitoring networks and methods, ambient concentrations and trends for ozone and PM (fine and coarse), including PM composition, and their precursors in Canada. Chapter 4 describes emissions reporting and inventories and also discusses sources, spatial distribution and trends and projections of emissions of smog precursors in Canada and to some extent in the US. Chapter 5 provides the status of and confidence in Canadian chemical transport models (CTMs), which represent the science behind emission–concentration (E–C) relationships. Chapter 6 provides a review of recent air quality modelling studies performed with current CTMs to calculate ozone, PM and deposition in Canada based on emission reduction scenarios.

Canada is a large country with diverse landscapes, climates, weather patterns and sources of pollution. For this reason, Chapter 7 provides a region-by-region perspective of the emissions, physical features, meteorology, and long-range transport that give rise to air quality conditions over distinct areas of Canada. On the opposite side of the scale, Chapter 9 reviews the features of transcontinental transport of pollutants across the Pacific to North America and how these enhance smog levels in Canada. The atmospheric science portion of the volume is complemented by a review of new scientific research discoveries that are or have the potential to modify our understanding of air pollution formation and transport (Chapter 8). These include

the effects of climate change on air pollution, the atmospheric boundary layer and its relationship to air pollution, and satellite observations of air quality constituents from space.

Chapters 10 and 11 review recent findings on the effects of smog on vegetation and materials, and visibility, respectively. Lastly, an overview of the role of economic valuation and recent progress in valuating the impacts of smog on the environment and human health is presented in Chapter 12.

13.5.2 Volume 2: Health Effects (Chapters 13–15)

This volume, prepared by Health Canada with input from several external contributors, builds upon the most recent previous Canadian and US assessments and critically evaluates relevant information that has become available since the earlier assessments up to 2007. The assessment of this information is critical to establishing the weight of evidence for the various health effects associated with ambient PM and ozone, and for supporting the use of concentration–response (C–R) relationships to estimate the health impacts of current air quality or the benefits from future ambient concentration changes.

Chapter 14 presents the scientific review and assessment of the health-related information on ambient PM. Exposure of the general population to ambient PM is covered in Section 14.1, while Section 14.2 discusses the dosimetry of inhaled particles in the respiratory tract. Sections 14.3 and 14.4 examine the results of toxicological studies of various types of PM in animals and humans, respectively. Sections 14.5 through 14.8 review the epidemiological literature, including studies of the association between acute exposure to fine ambient PM and health effects, reproductive and developmental endpoints, genetics, and health effects associated with chronic exposure to fine ambient PM. A risk characterization (Section 14.9) integrating key information from the prior chapters on exposure, dosimetry, and health effects of fine PM concludes the chapter.

Chapter 15 presents the corresponding scientific review and assessment of the health-related information on ground-level ozone, including exposure assessment (Section 15.1), dosimetry (15.2), toxicological studies in animals (15.3) and humans (15.4), acute exposure epidemiology (15.5), epidemiology of reproductive and developmental endpoints (15.6), of genetics (15.7), and of chronic exposure (15.8), followed by a risk characterization (15.9).

Chapters 1 and 13 set the context for each volume. The chapters in both volumes have been peer reviewed internally and externally by experts on the key subject areas assessed in the report. The external peer review, managed by an independent non-profit organization (TERA: Toxicological Excellence for Risk Assessment), focused on the validity of the selection of pertinent studies included in the chapters, the potential need for additional information to be included, and the quality of the analysis, summarization and interpretation of the literature.

13.5.3 Summary Report of Highlights and Key Messages

The information contained within the Assessment was tailored to be focused on policy-relevant issues as collectively identified by the scientific and policy communities at the onset of this review. A summary of the most important results, focused on certain specific aspects of the science and related risk management issues, is contained in a separate piece entitled the *Canadian Smog Science Assessment Highlights and Key Messages* (Environment Canada and Health Canada, 2011).

13.6 References

Canada-US. 2004. Canada-United States Transboundary PM Science Assessment. A report by the Canada-US Air Quality Committee Subcommittee 2: Scientific Cooperation. Available at <http://www.epa.gov/airmarkets/progsregs/usca/docs/transboundary.pdf>.

Environment Canada. 2001. Precursor Contributions to Ambient Fine Particulate Matter in Canada. Meteorological Service of Canada, Toronto Ontario.

Environment Canada. 2011. Canadian Smog Science Assessment. Final Supporting Document. Volume 1. Atmospheric Science and Environmental Effects. Available upon request from enviroinfo@ec.gc.ca.

Environment Canada and Health Canada. 2011. Canadian Smog Science Assessment: Highlights and Key Messages. ISBN 978-1-100-19063-1. Cat. No.: En88-5/2011E.

Health Canada. 2011. Canadian Smog Science Assessment. Final Supporting Document. Volume 2. Health-Related Chapters. Available upon request from air@hc-sc.gc.ca.

Health Canada and Environment Canada. 1999a. National Ambient Air Quality Objectives for Particulate Matter Part 1: Science Assessment Document. Ottawa, ON:10-1 to 10-28.

Health Canada and Environment Canada. 1999b. National Ambient Air Quality Objectives for Ground-Level Ozone: Science Assessment Document. Ottawa, ON. Cat. No. En42-17/7-1-1999E.

United States Environmental Protection Agency (US EPA). 2004. Air Quality Criteria for Particulate Matter. Washington, DC: Publication No. EPA 600/P-99/002aF-bF.

United States Environmental Protection Agency (US EPA). 2006. Air Quality Criteria for Ozone and Related Photochemical Oxidants. Washington, DC: Publication No. EPA 600/R-05/004aF.

Chapter 14: Health Effects of Ambient Fine Particulate Matter

14.1 Exposure Assessment

14.1.1 Introduction

This section examines the current knowledge regarding exposure of Canadians to ambient PM. While PM from indoor sources is discussed briefly, this document is largely focused on PM from ambient sources, in order to support the assessment and management of sources that affect ambient air quality in Canada. This support includes informing the evaluation and establishment of ambient air quality standards/objectives for fine PM.

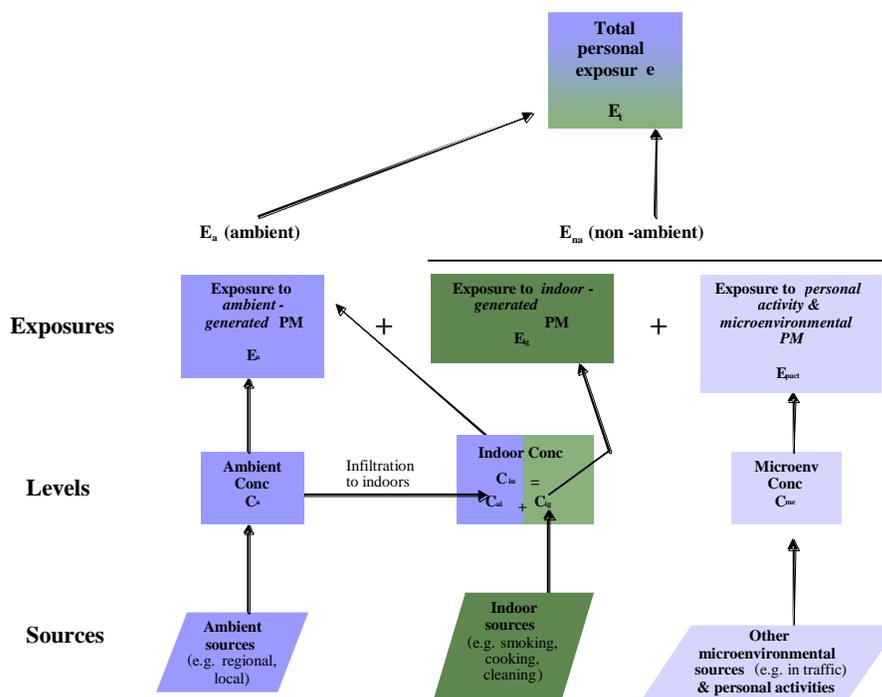
Section 14.1.2 briefly describes a framework for understanding personal exposure to PM (in particular, ambient-generated PM), while Section 14.1.3 summarizes the findings of the 1999 PM SAD and US EPA 2004 PM AQCD assessments regarding human exposure to PM. Section 14.1.4 provides a general overview of current levels of fine PM in Canada. Section 14.1.5 examines concepts and methods for studying personal exposure to PM and reviews the results of studies of personal exposure to PM, including PM_{2.5}, PM₁₀, coarse PM (PM_{10-2.5}), continuous PM measures and ultrafine PM. Section 14.1.6 reviews the results of personal exposure studies of chemical constituents of PM, in Canada, the US and Europe. Section 14.1.7 discusses the sources and factors affecting personal exposure to ambient-generated PM, including time-activity, the infiltration of ambient PM into indoor environments, and personal exposure levels of ambient and non-ambient PM. The section also summarizes information on the relationship between exposure to ambient and non-ambient PM with ambient PM levels. Section 14.1.8 discusses the relevance and implications of using fixed-site outdoor monitoring data in epidemiological studies as an indicator of exposure to PM of outdoor origin (fine particles as well as ultrafine and coarse particles), while Section 14.1.9 presents a summary and considerations with respect to exposure to PM.

14.1.2 Concepts in Exposure to Particulate Matter

Figure 14.1 visually summarizes human exposure to PM. Humans are exposed to PM as they go about their daily lives in various microenvironments (outdoors, indoors at home, work, school, in-vehicle etc), where each microenvironment typically has a different level of PM. Ambient PM is influenced by both regional (transported) and local sources. Ambient (central site) PM monitors are typically sited to represent background urban levels of PM in the community. Consequently, levels in specific outdoor microenvironments, such as traffic microenvironments (busy roadways or in-vehicle) are often not reflected in the levels measured at ambient monitors, but individuals are exposed to these higher PM levels during their time spent in these microenvironments. In indoor environments such as the home, PM levels are influenced by (a) ambient air that has infiltrated into the indoor environment and (b) indoor sources such as smoking, cooking, and cleaning. The PM in ambient, indoor and traffic microenvironments will differ in size distribution, chemical characteristics and most likely, toxicity, due to the varying sources and conditions affecting secondary transformation.

Personal exposure to PM has been measured for individuals in various studies in Canada, the US, Europe and Asia, using portable PM monitors/samplers that are worn by study participants as they go about their regular activities. As mentioned previously, ambient levels are typically measured by a fixed-site monitor located centrally in the community so as not to be unduly influenced by sources in the immediate vicinity of the site; this document refers to a measurement from this type of monitor as an “ambient” concentration. “Outdoor” concentrations are typically measured by a monitor located in the immediate vicinity of a participant’s residence. “Indoor” residential concentrations are typically measured using monitors located centrally in a living room or bedroom, not adjacent to a source such as a kitchen stove or space heater.

Figure 14.1 PM exposure framework



Regulatory frameworks, source, composition and probably toxicity are different for ambient and indoor generated PM. Therefore it is informative to separate personal exposure and indoor levels into these two different components: ambient generated PM and non-ambient generated PM (Wilson and Suh, 1997; Mage et al., 1999; Wilson et al., 2000; Wilson and Brauer, 2006). Because this document is being developed in support of ambient PM air quality standards/objectives, most attention will be placed on the ambient component of exposure. The estimated ambient component of personal exposure is an estimate of the amount of PM measured at an ambient or central site monitor that a person is exposed to while indoors (by exposure to ambient PM that has infiltrated indoors) and while outdoors. The estimated non-ambient component of personal exposure generally includes exposure to indoor source PM, exposure to PM generated from personal activities (e.g. cooking, cleaning) and exposure occurring in outdoor microenvironments that are not reflected in levels measured by a central site monitor or a monitor situated beside a home (such as traffic microenvironments). Two recent panel studies have shown the feasibility and usefulness of separating total personal

exposure into ambient and non-ambient components. In these studies, the ambient component of exposure to PM, but not total and/or non-ambient PM, was associated with respiratory and cardiac effects (Ebelt et al., 2005; Koenig et al., 2005). The results of these studies are described in more detail in Section 14.5.5.

14.1.3 Summary of Previous Assessments

14.1.3.1 Health Canada/Environment Canada 1999 PM SAD

The PM SAD of 1999 (Health Canada and Environment Canada, 1999) reviewed available information concerning human exposure to ambient PM. The infiltration of ambient PM into indoor environments was discussed and it was estimated that, in Canada, infiltration of coarse and fine PM would be about 50% of ambient levels, with some limited evidence that penetration of coarse PM was lower than fine PM. The authors noted that there was also evidence that larger particles ($>5\ \mu\text{m}$) settle out more easily but are easily resuspended, whereas these processes are minimal for particles $<1\ \mu\text{m}$ in diameter.

A number of studies that measured indoor and outdoor levels of PM, usually PM_{10} , were discussed, as well as a few personal exposure studies; no Canadian studies were available at that time. It was concluded that in areas where the ambient PM levels were high, such as Riverside, CA, average outdoor levels generally exceeded average indoor levels, whereas the reverse was often the case when ambient PM levels were lower. Indoor sources of PM were reported to include smoking as well as cooking, cleaning, kerosene heaters and wood stoves.

PM_{10} personal exposure studies, all from the US, most often found higher average personal exposure levels than indoor or outdoor levels. The difference between the personal and indoor/outdoor levels was attributed to a “personal cloud” of PM around individuals, created by generation and resuspension of mainly coarse PM through personal activities. A probabilistic model was used to estimate the distribution of PM_{10} personal exposure for the Canadian population, based on input distributions of ambient levels, census data, time-activity, indoor source strengths, microenvironmental levels and smoking prevalence. The average outdoor PM_{10} level for input to the model was $24\ \mu\text{g}/\text{m}^3$, while the predicted average PM_{10} indoor and personal exposure levels were $40\ \mu\text{g}/\text{m}^3$ and $39\ \mu\text{g}/\text{m}^3$, respectively.

The 1999 PM SAD concluded from the literature that indoor microenvironments were the most important contributors to overall personal exposure to PM and that generally, ambient PM levels were poorly correlated with personal exposure levels, though stronger correlations were found when based on repeated measurements from individuals (i.e. “longitudinal” correlations). The document concluded that ambient levels measured by an ambient monitor represented exposure of people in a community to PM of ambient origin, but underestimated average population exposures to total PM, and that the contribution of ambient particles to average indoor and personal exposure levels will vary by geographical location and climate as a consequence of different ambient levels and differences in such parameters as building air exchange rates (AERs).

14.1.3.2 US EPA 2004 PM AQCD

The US EPA 2004 PM AQCD provided a detailed review of the literature up to October 2002 relating to human exposure to PM. It laid out a framework for understanding the components of human exposure to PM and discussed ways of estimating the fraction of ambient PM found indoors (infiltration factor) and the fraction of ambient PM to which people are exposed (attenuation factor). Factors affecting the infiltration of PM into indoor environments and subsequent personal exposure to ambient PM were discussed, including particle size and AER,

which in turn varies with season and geographical location. The attenuation factor also depends on time-activity patterns, including how much time is spent outdoors. The US document also described methods being used to estimate the ambient and non-ambient components of both indoor levels and personal exposure.

The US EPA 2004 PM AQCD focused considerable attention on the usefulness of data from central site monitors in epidemiological studies of the health effects of air pollution. The document concluded that PM mass concentrations, especially fine PM, typically are distributed relatively uniformly in most metropolitan areas; therefore few central site monitors are needed to represent population average ambient exposures in community time-series or long-term cross-sectional epidemiological studies of PM. In pooled studies (where different subjects are typically measured only once), total PM exposure is usually not well correlated with daily ambient PM concentrations, due to high interindividual differences in exposure to non-ambient PM. However, in longitudinal studies (where each subject is measured for multiple days), individual, daily values of total PM personal exposure and the daily ambient PM concentrations are found to be highly correlated for some, though not all, subjects. A few researchers have found that the non-ambient component of exposure is generally independent of the ambient component and that there is no correlation between the levels of the ambient PM that has infiltrated indoors and the indoor-generated PM concentrations. The AQCD concluded it is reasonable to assume that non-ambient PM exposure will normally have little correlation with ambient PM concentration and that non-ambient PM exposure is not expected to affect the relative risk (RR) determined by a regression of health responses on ambient PM concentration. Also, in time-series analyses of pooled or daily health data, ambient PM exposure rather than total personal PM exposure will have the stronger association with ambient PM concentration.

The US EPA 2004 PM AQCD concluded that exposure measurement errors are not expected to influence the interpretation of findings from either the chronic or time-series epidemiologic studies that have used ambient concentration data, as they include sufficient adjustments for seasonality and key confounders. The expectation, based on statistical modelling considerations, is that these exposure measurement errors or uncertainties will most likely reduce the statistical power and make it more difficult to detect any air-pollution-related health effect. Based on data from one study, the authors showed that “the error introduced by using ambient PM concentrations as a surrogate for ambient PM exposure biases the estimation of health risk coefficients low by the ratio of ambient PM exposure to ambient PM concentration (called the attenuation factor). However, the health risk coefficient determined using ambient PM concentrations provides the correct information on the change in health risks that would be produced by a change in ambient concentrations.”

14.1.4 Recent Ambient Levels of Fine PM in Canada

Information and data from ambient monitoring of fine PM in Canada are discussed in detail in Chapter 3 (Ambient Measurements and Observations) of the companion volume of this assessment, written by Environment Canada (Environment Canada, 2011). The following information has been taken from that report, or extracted from the summary report of this assessment (Environment Canada and Health Canada, 2011). Readers requiring more detail are referred to these documents.

NAPS network sites have been measuring both PM_{2.5} and PM_{10-2.5} particle mass since 1984 using dichotomous samplers. As of 2006, there were 27 dichotomous samplers operating at NAPS sites, supplemented by an additional 13 US EPA federal reference method samplers measuring only PM_{2.5}. There was also a much larger TEOM network of PM_{2.5} monitors (>100

sites). The following discussion emphasizes the findings for PM_{2.5}, which is the size fraction that is especially (although not exclusively) harmful to human health.

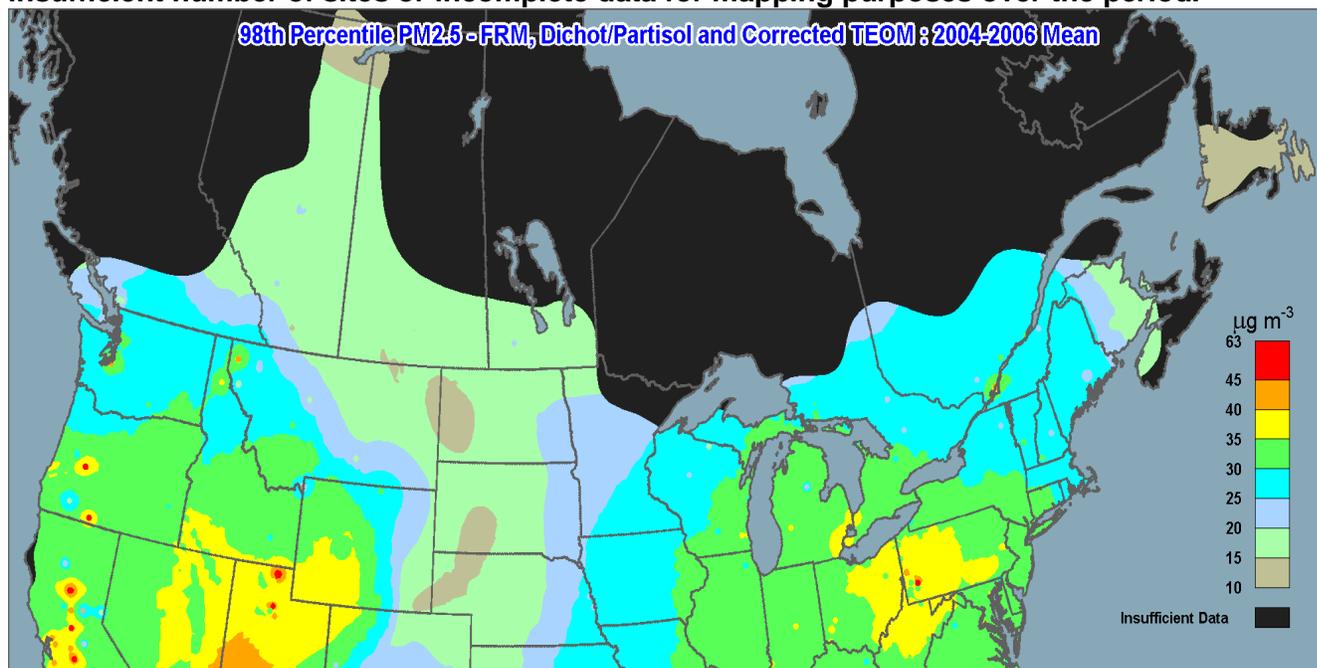
The spatial pattern of ambient PM_{2.5} levels across the country in 2004–2006 (Figure 14.2), as defined by the CWS metric, shows southern Ontario and southern Quebec having the highest concentrations (>25 µg/m³). This area is also part of a larger high concentration airshed that encompasses all of the eastern US. The highest levels in Canada over the 2004–2006 period occurred in some isolated areas under the influence of specific emission sources, but mainly in the Great Lakes region, particularly in southwestern Ontario, where densely populated urban sites experienced levels above the CWS. Across southern Quebec and eastern Ontario, PM_{2.5} concentrations were generally below the CWS target, with the exception of some specific communities influenced by local industries and large urban centres, highlighting the potential for emissions to lead to localized high levels. There are uncertainties in the exact levels and local details of the spatial distribution of PM_{2.5} (Figure 14.2) over some areas of the country because of a lack of PM_{2.5} measurement sites. However, on a broad scale Figure 14.2 provides a general picture of the spatial pattern.

To track the occurrence of high PM_{2.5} concentration events across the country, the number of days per month in which the daily 24-h average of PM_{2.5} concentrations exceeded 30 µg/m³ was counted over the period 2001–2005 at sites across Canada. Days with PM_{2.5} concentrations >30 µg/m³ can occur any month of the year, but sites in southern Ontario and southern Quebec experienced the greatest frequency of days >30 µg/m³ in summer, followed by winter. At the western sites, the highest frequency of days occurred in the summer, associated with the occurrence of forest fires.

The frequency of regional scale episodes, defined as days where 33% of air monitoring sites in a region record 24-h average PM_{2.5} concentrations above 30 µg/m³, was also determined for the 2001–2005 period. Regional scale episodes of PM_{2.5} occurred in both winter and summer. The greatest frequency of regional scale episodes also occurred in Ontario, followed by Quebec, with high PM_{2.5} values often persisting for several days. Summer PM_{2.5} episodes in Ontario and Quebec were often associated with ozone values greater than the CWS target of 65 ppb, whereas winter episodes were solely a result of high levels of PM_{2.5}. Regional episodes were infrequent in the Prairies and the Lower Fraser Valley of British Columbia, and the events that did occur were associated with forest fires. Although some areas may not experience frequent regional episodes, they may still experience days when PM_{2.5} levels are considered high locally, which would produce an increase in health effects and a decline in visibility relative to average conditions.

Levels of PM_{2.5} vary considerably by season within a region as observed through the analysis of PM_{2.5} daily peaks and averages measured at monitoring sites. In southern Atlantic Canada, the daily peaks and averages in PM_{2.5} are higher in summer than in winter. This seasonal difference is due to more intense sunlight leading to greater sulphate concentrations, and more frequent favourable wind patterns that carry pollutants from sources in the southwest. In winter, PM_{2.5} levels are influenced more by local sources such as residential wood combustion. Across southern Quebec and eastern Ontario, daily peaks and averages are higher in winter than summer. In particular, over the southern Great Lakes region, the highest daily averages occur in winter, as colder temperatures favour the formation and build-up of ammonium nitrate on the particles and meteorological conditions result in less pollutant dispersion.

Figure 14.2 Spatial distribution of the 98th percentile 24-h PM_{2.5} concentrations ($\mu\text{g}/\text{m}^3$) across Canada and the US for 2004–2006. Areas in black depict where there is either an insufficient number of sites or incomplete data for mapping purposes over the period.



In Alberta, both PM_{2.5} peaks and averages are higher in the winter when cold and calm conditions lead to some of the highest concentrations of primary pollutants in Canada. In the Lower Fraser Valley, daily average levels are highest in late summer and early fall, with peaks in fall and winter. This is due to favourable meteorological conditions in the late summer and changes in local activities, including wood burning and space heating in the fall and winter. In the interior of British Columbia, levels also peak in the fall and winter where emissions from the frequent use of residential wood combustion play a role, along with strong inversions due to cold air pooling in the valleys and/or the trapping of air by the mountains. In Whitehorse, Yukon, daily averages are highest during the summer months, and annual variability at this site appears to be influenced by forest fires. In the winter, high PM_{2.5} levels occur due to woodsmoke.

The spatial pattern of the annual mean of PM_{2.5} concentrations in Canada is very similar to the spatial pattern of the CWS metric (Figure 14.2), with the highest concentrations ($>8 \mu\text{g}/\text{m}^3$) occurring in southern Ontario and southern Quebec.

14.1.5 Personal Exposure Levels

14.1.5.1 Overview of Methods for Determining Personal Exposure

Total personal exposure can be measured directly for individuals using portable monitors or can be estimated using personal exposure models. Direct measurement is carried out using portable monitors and pumps that participants carry for a specified time period (often 12, 24 or 48 h), with the air intake located near the nose/mouth area. Summary descriptions of some personal monitors have been compiled by Wallace (2006), the US EPA (2004), Hopke and Markowitz (2002) and Jantunen et al. (2002).

Studies involving direct measurement of personal exposure levels often also measure concentrations of PM indoors (residential and/or workplace), outdoors (outside residence and/or

workplace) and at one or more fixed ambient monitoring sites in the community being studied. These measurements are taken to examine relationships between personal exposure and the indoor, outdoor and ambient PM levels.

PM samplers can be filter-based, yielding a measurement of the mass of PM collected on the filter (and in some cases, allowing subsequent chemical or elemental analysis of the components of PM collected on the filter). These monitors draw air through a filter; PM collects onto the filter, which is weighed before and after the sampling period to provide a measure of the PM mass. This mass is divided by the volume of air sampled during the time period to provide an average concentration ($\mu\text{g}/\text{m}^3$) of PM. Alternatively, continuous methods, based on measurement of physical properties of particles, such as light-scattering, can yield either mass, volume, area, or particle count measurements. For the latter three measurements, mass can be estimated either by calibration of a given monitor with a reference standard of known density or by direct comparison with concurrent mass measurements.

Personal exposure studies have generally measured $\text{PM}_{2.5}$ (fine PM), PM_{10} (inhalable PM) or sometimes PM_4 or PM_5 (respirable PM). Personal exposure to coarse PM mass (e.g. $\text{PM}_{10-2.5}$) has been measured in a few studies either by subtraction of $\text{PM}_{2.5}$ from PM_{10} , or by direct measurement using recently developed personal coarse PM monitors. A few studies have measured personal exposure to UFPs. Further details of these studies are given below.

Personal exposure and indoor studies of PM have used a variety of instrumentation for ambient monitoring, including those samplers used for personal and/or indoor monitoring, such as Personal Exposure Monitors (PEMs) or Harvard Impactors. As well, studies often use data from government monitoring networks, which include filter-based instruments, often based on the EPA Federal Reference Method (FRM) for $\text{PM}_{2.5}$ or PM_{10} as well as dichotomous samplers (for $\text{PM}_{2.5}$ and $\text{PM}_{2.5-10}$) and continuous monitors (for $\text{PM}_{2.5}$ or PM_{10}). Ambient monitors used in the Canadian National Air Pollution Surveillance (NAPS) program have been discussed in more detail in Chapter 3 of the companion volume to this assessment, written by Environment Canada scientists (Environment Canada, 2011).

An alternative to direct measurement of personal exposure is modelling or estimation of average exposure over a certain time period, by summing, for each individual, the product of the time spent in each microenvironment by the known or estimated level of PM in each microenvironment. Probabilistic models use distributions of time-activity and microenvironmental concentrations to model variability and uncertainty in the input variables, resulting in a predicted population distribution of exposure. The US EPA 2004 PM AQCD provides a more detailed description of the types of exposure models that have been developed by various authors.

14.1.5.2 Summary of Personal Exposure Studies

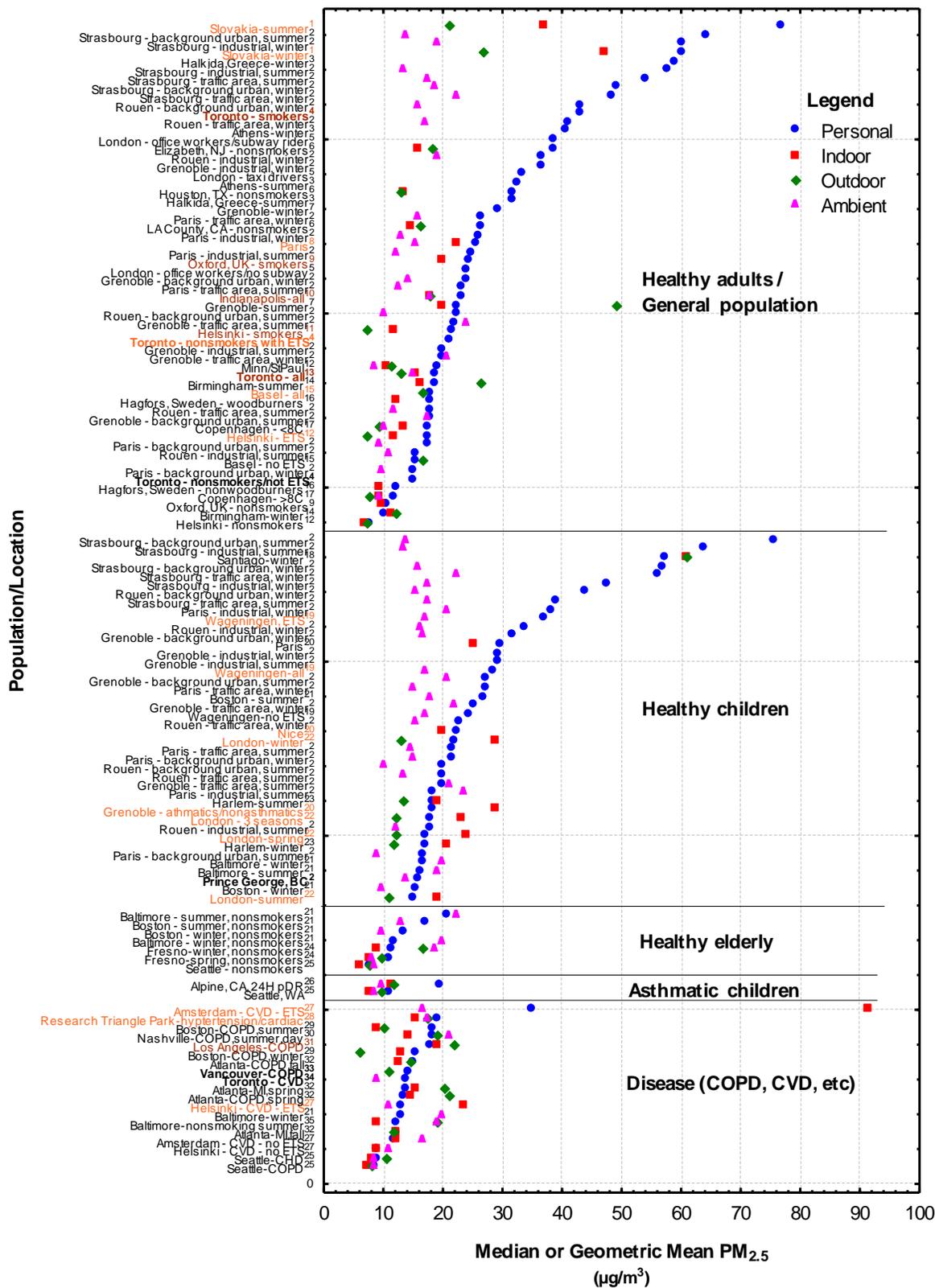
Personal exposure levels have been measured in studies from Canada, the United States and Europe. Typically these studies have measured personal, residential indoor, residential outdoor and/or central site ambient levels for each participant, often over a number of days. Some studies have been repeated over different seasons. A few large studies—notably in Toronto, ON; Indianapolis, IN; Helsinki, Finland; and Riverside, CA—have been carried out using probability sampling to get a statistically representative sample of the general population, which means that the study results can be extrapolated to the larger population being studied. Thus although the Toronto study included just 881 Toronto residents, the results, properly weighted by the inverse of the probability of selection, apply to the entire non-institutionalized population of Toronto at least 16 years of age (about two million residents.) Other “panel” studies have focused on subgroups including healthy, active adults, or subgroups based on age or disease state such as children, healthy elderly, and patients with cardiovascular disease (CVD) or COPD; these subgroups may have altered activity patterns that result in different exposure

patterns, in addition to increased susceptibility to PM exposure. In these studies, the non-representative method of selection of participants does not allow for results to be extrapolated beyond the sample itself, but it does allow for in-depth analyses of the results for that sample only. In the longitudinal studies, personal samples are taken repeatedly over a number of days along with indoor and outdoor samples, allowing for assessment of (a) levels and determinants of personal exposure; (b) relationships with indoor and outdoor levels; and (c) factors affecting the relationships between personal exposure and outdoor levels. These longitudinal (within-subject) correlations with ambient air are typically higher than cross-sectional (across-subject) correlations (Jannsen et al., 1999a). Some of these studies have estimated the proportion of total personal exposure from ambient sources (through exposure while outdoors as well as exposure to ambient-generated PM that has infiltrated indoors). These studies will be discussed in more detail in Section 14.1.7.

Many studies of personal exposure have been carried out at various locations in Canada, the US and Europe. The geometric mean (GM) or median personal, indoor, outdoor and ambient levels reported for these studies are presented graphically in Figure 14.3 for PM_{2.5} and Figure 14.4 for PM₁₀. Studies that included smokers are highlighted in brown, studies with participants who reported environmental tobacco smoke (ETS) exposure are highlighted in orange and Canadian studies are highlighted in bold. Section 14.1.5.1 discusses the Canadian studies; Section 14.1.5.2 discusses the US and European studies.

Many US and Canadian studies have employed a personal impactor based on a design by V. Marple (MSP Corp.) and variously known as the Marple PEM, the Harvard PEM, the SKC PEM, etc. Several studies have documented that the PEM has a small positive bias on the order of 16–18% compared with high-volume reference gravimetric samplers such as the dichotomous sampler (Williams et al., 2000a, 2000d; Liu L-JS et al, 2003). Since in many of these studies the same PEM is used not only for personal exposure but also both indoors and outdoors, the relative levels across microenvironments are unaffected by this bias, and will be unadjusted throughout this document.

Figure 14.3 Personal, indoor, outdoor and ambient PM_{2.5} levels from various studies (medians or geometric means)



References for Figure 14.3:

- ¹Brauer et al. (2000)
- ²Nerriere et al. (2005)
- ³Georgiadis et al. (2001)
- ⁴Crump (2000)
- ⁵Pfeifer et al. (1999)
- ⁶Meng et al. (2005a)
- ⁷Boudet et al. (2000)
- ⁸Mosqueron et al. (2002)
- ⁹Lai et al. (2004)
- ¹⁰Pellizzari et al. (2001)
- ¹¹Koistinen et al. (2001)
- ¹²Adgate et al. (2003)
- ¹³Pellizzari et al. (1999)
- ¹⁴Lachenmyer and Hidy (2000)
- ¹⁵Oglesby et al. (2000)
- ¹⁶Molnar et al. (2005)
- ¹⁷Sørensen et al. (2005a)
- ¹⁸Rojas-Bracho et al. (2002)
- ¹⁹Janssen et al. (1999a)
- ²⁰Zmirou et al. (2002)
- ²¹Koutrakis et al. (2005)
- ²²Wheeler et al. (2000)
- ²³Kinney et al. (2002)
- ²⁴Evans et al. (2000)
- ²⁵Liu L-JS et al. (2003)
- ²⁶Wu et al. (2005b)
- ²⁷Brunekreef et al. (2005)
- ²⁸Williams et al. (2003a, 2003b)
- ²⁹Rojas-Bracho et al. (2000)
- ³⁰Bahardori (1998)
- ³¹Linn et al. (1999)
- ³²Williams et al. (2002)
- ³³Ebelt et al. (2000)
- ³⁴Kim et al. (2005, 2006)
- ³⁵Williams et al. (2000a, 2000b)

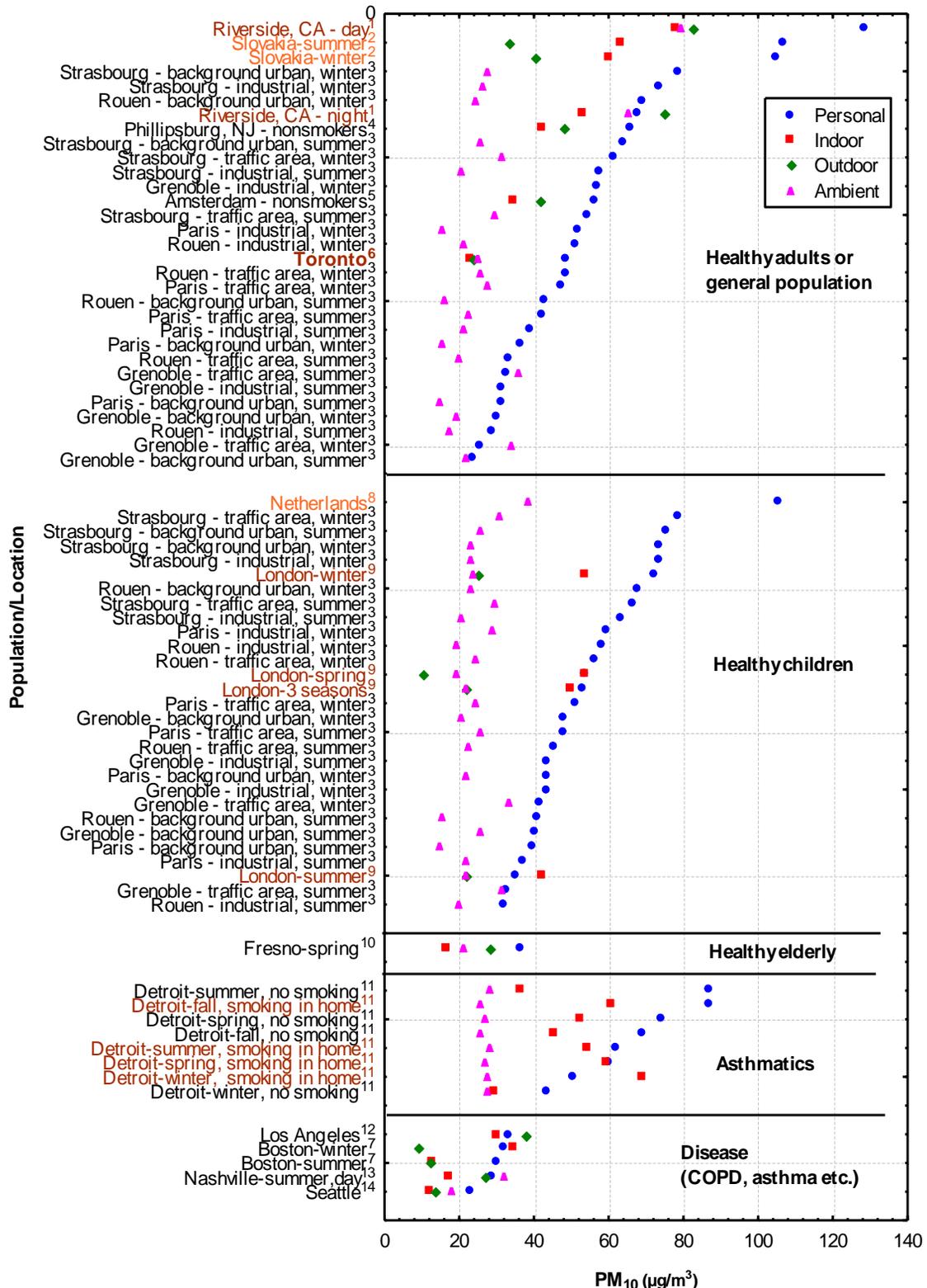
Notes:

orange text—some/all participants reported exposure to ETS

brown text—some/all participants are smokers

bold text—Canadian studies

Figure 14.4 Personal, indoor, outdoor and ambient PM₁₀ levels from various studies (medians or geometric means)



References for Figure 14.4:¹Clayton et al. (1993), ²Brauer et al. (2000), ³Nerriere et al. (2005), ⁴Lioy et al. (1990), ⁵Janssen et al. (1998), ⁶Pellizzari et al. (1999), ⁷Rojas-Bracho et al. (2002), ⁸Janssen et al. (1997), ⁹Wheeler et al. (2000), ¹⁰Evans et al. (2000), ¹¹Keeler et al. (2002), ¹²Linn et al. (1999), ¹³Bahadori (1998), ¹⁴Jansen et al. (2005)

14.1.5.3 Canadian Studies

Only a few personal exposure studies have been carried out in Canada. Most have measured personal exposure to PM_{2.5} or PM₁₀; some studies also measured the SO₄²⁻ and EC levels on the PM_{2.5} filters. One study (Stieb et al., 1998) measured only personal exposure to hydrogen (H⁺), SO₄²⁻, nitrate (NO₃⁻) and ammonium (NH₄⁺) ions. The most comprehensive study with direct measurements of personal exposure to PM in Canada was a large probability study of Toronto residents carried out in 1995–1996 by RTI International (Pellizzari et al., 1999; Crump, 2000) under contract with Ethyl Corp. This study was designed to look at personal manganese (Mn) exposures associated with the use of MMT (methylcyclopentadienyl manganese tricarbonyl), a gasoline additive. The study used a probability sampling design, in which subjects were selected to provide a representative sample of the Toronto population. While the focus was on assessing personal exposure to PM Mn, the study also provided data on PM mass. Four other studies looked at specific groups; each of these measured only personal exposure and ambient levels (no indoor levels). The studies were smaller in scale and did not use probability sampling designs, so the results cannot be extrapolated to a larger population. One of these studies, of 15 healthy children, 10–12 years of age, was carried out in Prince George, BC, in February–March 2001 (Noullett et al., 2006). The three other studies looked at adults with pre-existing health conditions. One study was carried out in St. John, NB, in the summer of 1995, involving 21 non-smoking adults with cardiorespiratory disease. Another study was carried out in Vancouver, BC, in 1998, involving 16 non-smoking adults with COPD (ages 54–86) (Ebelt et al., 2000). A third study was carried out in Toronto between 1999 and 2001, involving 27 non-smoking adults with heart disease (ages 49–80) (Kim D et al., 2005, 2006).

Brief summaries of the levels of exposure found in each of these studies are provided below. Discussion of the levels of the PM chemical components is provided in Section 14.1.6. In general, the PM_{2.5} personal exposure and ambient levels were in the lower range of levels seen in other studies in the US and Europe (Figure 14.3). In each study the median personal exposure levels were higher than ambient levels. Personal exposures generally had a skewed distribution and were more variable than ambient levels. However, the ability to estimate PM exposure for the Canadian population is limited by the lack of probability design studies in different regions of the country during different seasons.

14.1.5.3.1 Toronto RTI Study (1995–1996)—general population

This study included 881 smoking and non-smoking participants selected using a stratified probability-weighted design to reflect the Toronto population; they provided 922 3-d PM_{2.5} personal exposure samples collected using Marple PEMs. In addition, 183 indoor samples and 178 outdoor residential samples were collected using Marple PM_{2.5} PEMs. The estimated distribution of 3-d PM_{2.5} personal exposures for Toronto residents had a median of 18.7 µg/m³ and 95th percentile of 86.6 µg/m³. The median PM_{2.5} personal exposure for non-smokers (17 µg/m³) was considerably lower than for smokers (43.0 µg/m³). The median of the indoor levels was 15.4 µg/m³; outdoor (at home) levels, 13.2 µg/m³; ambient levels, 16 and 14 µg/m³ (two fixed sites), respectively (Pellizzari et al., 1999, 2001; Crump, 2000). For comparison, the mean PM_{2.5} concentration averaged over all NAPS dichotomous monitors for 1995 was 14.2 µg/m³ and for 1996 was 13.2 µg/m³ (M. Smith-Doiron, pers. comm.). Simulation models were used to estimate the distribution of annual personal exposures based on the 3-d exposures (Clayton et al., 1999); the median of this distribution was 23.2 µg/m³, and the 95th percentile was 62.9 µg/m³. As found in many other studies of healthy individuals, personal exposures to PM_{2.5} generally exceeded the indoor levels, which in turn exceeded outdoor levels.

Personal PM₁₀ levels were also measured for 2 summer months in 1995; the median value was 48.5 µg/m³. The median indoor PM₁₀ level was 23.1 µg/m³, median outdoor PM₁₀ was 23.6

$\mu\text{g}/\text{m}^3$ and the median ambient levels were 27 and 23 $\mu\text{g}/\text{m}^3$ at two fixed sites. For comparison, the mean ambient PM_{10} levels averaged over all NAPS dichot monitors were 23.8 $\mu\text{g}/\text{m}^3$ for 1995 and 25.5 $\mu\text{g}/\text{m}^3$ for 1996 (M. Smith-Doiron, pers. comm.).

14.1.5.3.2 St. John (July–August 1995)—older adults with cardiorespiratory illness

Stieb et al. (1998) studied 21 former or never-smokers with cardiorespiratory disease, aged 49–85, who wore personal annular denuders for approximately 8-h periods (generally 7 a.m. to 6 p.m.) for up to 4 d. No PM mass measurements were taken. For each day that personal samples were collected, a sampler was also operated at the fixed site for the same duration as the personal samples. Teflon filters were analyzed for acidity (H^+) and for SO_4^{2-} , NO_3^- and NH_4^+ using ion chromatography. The mean personal SO_4^{2-} (2.9 $\mu\text{g}/\text{m}^3$ (range 0.5–16.4)) was lower and less variable than the mean ambient SO_4^{2-} level (4.7 $\mu\text{g}/\text{m}^3$ (range 1.4–214)). Similarly, the mean personal acidity (H^+) (0.02 $\mu\text{g}/\text{m}^3$ (range 0.01–0.08)) was lower than the mean ambient level of 0.4 $\mu\text{g}/\text{m}^3$ (range 0.01–0.12).

14.1.5.3.3 Prince George (February–March 2001)—healthy children

This study (Noullett et al., 2006) involved 15 healthy children; each child provided up to ten 24-h personal $\text{PM}_{2.5}$ samples collected using Harvard PEMs; these samples were also analyzed for SO_4^{2-} and light-absorbing carbon. The median 24-h $\text{PM}_{2.5}$ personal exposure was 16 $\mu\text{g}/\text{m}^3$, with a range of 3–179 $\mu\text{g}/\text{m}^3$. The median was calculated after the removal of the two largest values, which the authors claimed were due to cooking episodes in the homes; however, these “outliers” may reflect the range of conditions that exist for some people. The median ambient $\text{PM}_{2.5}$ level measured during the same time period, also using Harvard PEMs, was 14 $\mu\text{g}/\text{m}^3$ (range 1–61 $\mu\text{g}/\text{m}^3$). Again, personal exposure levels were slightly higher and more variable than ambient levels; indoor levels were not measured.

14.1.5.3.4 Vancouver (April–September 1998)—non-smoking adults with COPD

This study (Ebelt et al., 2000; Wilson and Brauer, 2006) looked at 16 non-smoking adults with COPD, aged 54–86 years. Each participant provided seven 24-h personal exposure $\text{PM}_{2.5}$ samples, using PEMs (MSP Corp.), with each sample approximately 1.5 weeks apart. Ambient $\text{PM}_{2.5}$ samples were collected using Harvard Impactors. The GM of the personal $\text{PM}_{2.5}$ 24-h exposures was 14.3 $\mu\text{g}/\text{m}^3$, which was higher than the GM of the concurrent 24-h ambient $\text{PM}_{2.5}$ levels (10.8 $\mu\text{g}/\text{m}^3$). The range of personal exposures was also considerably larger than ambient levels (2.2–90.9 $\mu\text{g}/\text{m}^3$ vs. 4.2–28.7 $\mu\text{g}/\text{m}^3$, respectively). The GM of the 24-h ambient PM_{10} levels was 16.0 (range 6.0–51.0 $\mu\text{g}/\text{m}^3$). Ebelt reported both cross-sectional and longitudinal correlations of personal with ambient $\text{PM}_{2.5}$. The cross-sectional correlation ($n = 106$) was 0.15; the median of the 16 longitudinal correlations was 0.48.

14.1.5.3.5 Toronto (August 1999–November 2001)—non-smoking adults with heart disease

This study (Kim D et al., 2005, 2006) involved 27 non-smokers, aged 49–80 years, who provided five to ten 24-h personal $\text{PM}_{2.5}$ exposure samples, collected using the Chempass Personal Sampling unit with 4.0 L/min PEMs. The median personal exposure was 14 $\mu\text{g}/\text{m}^3$. The median ambient level measured at the Gage Institute in downtown Toronto (9 $\mu\text{g}/\text{m}^3$), measured by a tapered element oscillating microbalance (TEOM) sampler, was considerably lower than the median personal exposure level. Based on the results from co-located Chempass and TEOM samplers, regression of the personal Chempass data onto the TEOM data ($n = 14$) resulted in a slope of 1 with an intercept of 0.33 ($R^2 = 0.93$), so the personal–ambient differences can not be attributed solely to instrument differences. As in other studies, personal exposures were considerably more variable than ambient levels (range 4–503 $\mu\text{g}/\text{m}^3$ vs. 0–42 $\mu\text{g}/\text{m}^3$ respectively).

14.1.5.4 US and European Studies

14.1.5.4.1 $PM_{2.5}$ and PM_{10}

Figures 14.3 and 14.4 include summary statistics for personal, indoor, outdoor and ambient levels from US and European personal exposure studies for $PM_{2.5}$ and PM_{10} , respectively. Most studies in these figures have not used probability sampling, except for the PTEAM study in Riverside, CA, and the EXPOLIS study in Europe (Helsinki). For healthy adults and children, median personal exposure levels generally exceeded median indoor levels, which in turn exceeded median outdoor levels. It is interesting to note that the difference between personal exposure and ambient $PM_{2.5}$ levels is larger in primarily European countries.

These figures also show a general trend for lower personal exposure levels and smaller personal–ambient differences in studies of healthy elderly, and children and adults with pre-existing disease conditions. However, given the lack of general population studies in the same locations for comparison it is unclear whether the lower personal exposure levels in these studies is due to modified time-activity patterns because of disease or age rather than conditions specific to those locations. It has been hypothesized that some elderly individuals and individuals with disease conditions have lower exposures to indoor-generated PM due to limitations in activities such as cooking and cleaning. Those populations living in residences/institutions with mechanical filtration systems would have less exposure to infiltrated PM. As well, they spend less time in outdoor or transit environments (Section 14.1.7.1), resulting in lower direct exposure to ambient PM. Consequently their exposure to indoor- and outdoor-generated PM may be reduced in comparison to the general population. In healthy adults, indoor exposures are more variable and can dominate personal exposures (compared with ambient exposures).

14.1.5.4.2 $PM_{10-2.5}$

Personal exposure to coarse PM has been measured in only a few studies, none of which were in Canada. Sarnat et al. (2000), in a study of 15 non-smoking elderly in Baltimore, MD, sampled during the summer and winter of 1998–1999, found a median summertime $PM_{10-2.5}$ personal exposure level of $6.7 \mu\text{g}/\text{m}^3$ (max $24.8 \mu\text{g}/\text{m}^3$) compared with an ambient median of $8.1 \mu\text{g}/\text{m}^3$ (max $14.5 \mu\text{g}/\text{m}^3$). In the winter, the median personal exposure level was $8.2 \mu\text{g}/\text{m}^3$ (max $47.6 \mu\text{g}/\text{m}^3$), compared with an ambient median of $5.2 \mu\text{g}/\text{m}^3$ (max $24.2 \mu\text{g}/\text{m}^3$). Personal exposure samples were collected using modified 4.0 L/min PEMs.

Rojas-Bracho et al. (2000, 2004) measured personal, indoor and outdoor levels of $PM_{10-2.5}$ in 18 Boston, MA, non-smokers with COPD over 6 d during the winter of 1996–1997 and 6–12 d in the summer of 1996. Personal exposure levels (12-h) were higher in the winter (median $14.4 \mu\text{g}/\text{m}^3$ (max $103.3 \mu\text{g}/\text{m}^3$)) than in the summer (median $10.4 \mu\text{g}/\text{m}^3$ (max $93.9 \mu\text{g}/\text{m}^3$)). The median indoor level was higher than the personal level in the winter (indoor, $26.6 \mu\text{g}/\text{m}^3$ (max $255.3 \mu\text{g}/\text{m}^3$)) but not in the summer (indoor, $8.2 \mu\text{g}/\text{m}^3$ (max $78.3 \mu\text{g}/\text{m}^3$)). Outdoor levels were lower than personal and indoor levels during both seasons (outdoor winter median, $7.4 \mu\text{g}/\text{m}^3$ (max $63.5 \mu\text{g}/\text{m}^3$); outdoor summer median, $5.9 \mu\text{g}/\text{m}^3$ (max $53.1 \mu\text{g}/\text{m}^3$)). Personal exposure samples were collected using modified 4.0 L/min PEMs.

14.1.5.4.3 Continuous PM measures (personal DataRam)

A number of studies have been carried out using the personal DataRAM (pDR), which provides continuous PM measures (Howard-Reed et al., 2000; Quintana et al., 2001; Lanki et al., 2002; Delfino et al., 2004; Allen et al., 2004; Wu et al., 2005a, 2005b; Wallace et al., 2006a). This instrument uses a light scattering photometer (nephelometer) to measure real-time airborne particle concentrations. It responds to particles 0.3–10 μm ; however it is most sensitive to particles 0.5–2 μm (US EPA, 2004; Wallace, 2006). As the pDR overestimates PM mass

compared with PM_{2.5}, data from these studies have not been included in Figure 14.3 except for that of Wu et al. (2005b), who calibrated the pDR results with a co-located filter-based Harvard Impactor (in a study of 19 asthmatic children in Alpine, CA).

Across the studies, the mean values ranged from 15.5 µg/m³ in a study of 28 elderly CVD patients in Helsinki, Finland (Lanki et al., 2002) to 47.5 µg/m³ in a study of 10 non-smoking adults in San Diego, CA (Quintana et al., 2001). Delfino et al. (2004) and Wu et al. (2005b) report on the results from a study of 19 asthmatic children in Alpine, CA, measuring concurrent personal, indoor, outdoor and ambient pDR1000 levels during fall 1999 and spring 2000. As with many mass-based PM studies, the mean 24-h personal exposure (24.2 µg/m³) was higher than mean indoor (12.4 µg/m³), outdoor (12.6 µg/m³) and ambient (10.8 µg/m³) levels. Personal 24-h averages were also more variable than indoor, outdoor or ambient levels, as reflected in the maximum averages: personal 72 µg/m³, indoor 35 µg/m³, outdoor 32 µg/m³ and ambient 20 µg/m³. Wallace et al. (2006a) also found the mean personal 24-h exposure (33.3 µg/m³) was higher than the mean indoor 24-h concentration (29.8 µg/m³) in a study of 37 patients with hypertension or implanted defibrillators in Research Triangle Park, NC.

The continuous monitors are very useful in giving information about peak levels that people encounter, as seen by looking at the maximum levels found for shorter averaging times. They can also show how exposures vary over the day, and can identify sources of exposure, especially indoor sources that are brief and intermittent, such as cooking, cleaning or grooming activities. These findings are not possible using 12- or 24-h sampling times. For instance, in a study of asthmatic children in Alpine, CA, Delfino et al. (2004) reported data for varying averaging times, including the last 2 h and last 24 h. The means were similar (34.4 vs. 37.9 µg/m³, respectively); however, the maximum values were much higher for the 2-h averaging time (305.3 vs. 113.8 µg/m³, respectively). The maximum value of the 1-h max during the last 24 h was 996.8 µg/m³ (90th percentile 292.4 µg/m³). In the same study, Wu et al. (2005b) reported the maximum 15-min personal pDR (adjusted for equivalence with a mass-based Harvard Impactor) was 1311 µg/m³, while the maximum 24-h pDR was 72 µg/m³. Similarly, Lanki et al. (2002), in a study of elderly participants with CVD, found a maximum 24-h average of 112 µg/m³ but a maximum 1-h average of 855 µg/m³. In a seven-city study of asthmatic children in the US, every city had some 1-h indoor levels exceeding 1000 µg/m³ (Wallace et al., 2003a).

14.1.5.4 Ultrafine particles

UFPs are typically measured using particle counters, providing particle number (PN) data rather than particle mass data. There are few studies that have measured personal exposure levels for UFPs; a few others have looked at microenvironmental levels. Vehicular traffic is one of the major sources of UFPs, so most studies looking at them have examined levels while participants were in traffic microenvironments, including roadside and in-vehicle studies. Two personal exposure studies have looked at personal exposure to UFPs while travelling in traffic microenvironments. Vinzents et al. (2005) measured UFP personal exposure in a study of 15 healthy non-smoking subjects in Copenhagen, Denmark, looking at the relationship between UFP exposure and oxidative DNA damage. UFP exposure was monitored using condensation particle counters (10–1000 nm size range, model TSI 3007, TSI Inc.), which were worn by participants for six 18-h weekday periods from March to June 2003. On five of the six days, participants were asked to bicycle in central Copenhagen on a 20-km predefined route during morning and/or afternoon rush hours (mean time 93 ± 15 min). Another day included the same workload/intensity on an ergometer bicycle indoors with minimal UFP exposure. The authors report that the GM (geometric standard deviation) UFP exposure while on the bicycle route (32,400 (1.49) particles/cm³) was greater than during other outdoor activities (19,600(1.78) particles/cm³) or while indoors (13,400(1.96) particles/cm³).

In a scripted activity study, Kaur et al. (2005) investigated personal exposure to PM_{2.5}, UFP counts and carbon monoxide (CO) in central London, England. Four volunteers were asked to follow scripted routes in central London via walking, cycling, car (gas), taxi (diesel) or bus (diesel) while carrying sampling equipment. Personal PM_{2.5} samples were measured with a high-flow sampler (Adams et al., 2001a, 2001b) and UFPs 0.02–1.0 µm were measured using a P-Trak model 8525 (TSI Inc.). Samples were taken for the duration of each scripted route; the sample duration was a minimum of 18 min, but the average or maximum sampling duration was not provided. The overall average PM_{2.5} exposure was 33.6 µg/m³ (range 5.3–77.5 µg/m³) and significant differences were found between transport modes. Exposure during walking (mean 27.5 µg/m³ (14.3)) was significantly lower than exposure by car (38.0 µg/m³ (14.1)) or taxi (41.6 µg/m³ (14.7)). The UFP count ranged from 36,474 to 178,601 particles/cm³, 1-sec counts averaged over the sampling duration (one circuit). The lowest count occurred while on the walking circuit (mean 67,773 particles/cm³ (SD 23363)); the highest was on the bus circuit (mean 101,364 particles/cm³ (SD 24336)). The other three modes were similar (mean 88,101 (SD 31,291) particles/cm³). The personal exposure from walking was significantly lower than cycling, on bus and in car. The correlation between personal PM_{2.5} and personal UFP count was moderate (r = 0.5, p < 0.01). The correlation between UFP count and CO was higher (r = 0.7). Much lower levels were found at the roadside and at urban background monitors.

A third study was carried out involving nine young persons (aged 9–19) and 10 older patients with lung function impairments (aged 42–79) in Taiwan, looking at the relationship between personal exposure to UFPs and heart rate variability (HRV) (Chan et al., 2004). The youths carried a P-Trak UPC (Model 8525, TSI Inc.) while technicians accompanied the older participants between 0700 h and 2300 h for one monitoring period per participant. The UFP personal exposures for the young adults (based on 5-min averages) averaged 23,000 particles/cm³, with a range of 6000–350,000 particles/cm³. The elderly participants had a mean exposure of 25,500 particles/cm³ with a range of 1700–211,000 particles/cm³. UFP personal exposures were associated with impacts on a number of heart rate indices.

Studies of roadside or in-vehicle PM levels generally have found significant elevations of UFPs in both of these microenvironments (Zhu et al., 2002a, 2002b; Levy et al., 2003; Reponen et al., 2003; Sioutas et al., 2005). Studies in North America generally report decreased roadside concentrations with increasing distance from motorways, with particle sizes increasing with distance from vehicle traffic (Zhu et al., 2002a, 2002b, 2006; Levy et al., 2003; Riediker et al., 2003, 2004a; Westerdahl et al., 2005). For example, Zhu et al. (2002a, 2002b, 2006) measured UFP concentrations ranging from 200,000 particles/cm³ at 17 m downwind of Los Angeles, CA, freeways to 40,000 to 50,000 particles/cm³ at 300 m downwind. Levy et al. (2003) found roadside UFP levels ranging from 11,000 to 53,000 particles/cm³ at a distance of 25–75 m downwind of a Boston, MA, freeway. Westerdahl et al. (2005) monitored UFPs, nitrogen oxides (NO_x), black carbon (BC) and polycyclic aromatic hydrocarbons (PAHs) using an electric vehicle to carry the monitoring equipment throughout various locations in Los Angeles. Average concentrations of UFPs varied strongly by location, road type and truck traffic volumes, suggesting a positive relationship between concentrations and truck traffic density. UFP concentrations were higher than the urban background measurements by at least an order of magnitude in the freeway affected by diesel traffic or the mostly gasoline engine freeway. Diesel-powered vehicles were often a major source of high UFP count concentrations, especially when being directly followed.

A study carried out in three US cities in 2003–2004 looked at the benefits of various PM emissions controls on the in-cabin PM levels in school buses (Hill et al., 2005). Cabin levels of ultrafine PM were well above and many multiples of ambient levels; however, the authors note that there was significant variability in the data, making it difficult to generalize about exposure

levels in the school buses. The authors concluded that the use of a diesel particulate filter, ultralow sulphur diesel fuel and a closed-crankcase filtration device (Donaldson Spiracle) resulted in a comprehensive elimination of UFPs, BC, PAHs and PM_{2.5} in the cabin as well as at the curbside outside the bus (i.e. outside the schools).

14.1.6 Chemical Constituents of Personal Exposure Samples

14.1.6.1 Elemental and Organic Carbon

Carbon is present in PM primarily as organic carbon (OC), which is made up of many individual organic compounds, and elemental carbon (EC), which is operationally defined as all carbon not present as OC or carbonate/bicarbonate ion (Schauer, 2003). In the ambient environment, motor vehicle exhaust is a major source of EC and OC; diesel-fuelled vehicles produce particles high in EC content and gasoline-fuelled vehicles produce particles high in OC content (Watson et al., 1994). During the winter months residential wood burning also contributes to ambient EC levels (Kocbach et al., 2006). Indoor EC is primarily of ambient origin, with indoor combustion sources such as cooking and smoking contributing mainly to OC levels (Long et al., 2000; Cao et al., 2005). In the ambient environment, EC is present primarily in fine (0.056–1.8 µm, dominant peak at 0.32–0.56 µm) and ultrafine (0.05–0.1 µm) PM (Sodeman et al., 2005; Huang et al., 2006, respectively), whereas OC is present predominantly in fine (0.056–1.8 µm, dominant peak at 0.32–0.56 µm) and coarse (1.8–18 µm) particles (Huang et al., 2006).

To date, personal PM exposure studies have generally focused on EC, which is often used as a marker for traffic emissions. A number of studies (Brunekreef et al., 2005; Wichmann et al., 2005; Van Roosbroeck et al., 2006) have used measures of light absorption (a) termed “black smoke,” “black carbon,” or “light-absorbing carbon” as surrogate measures of EC, calculated using the reflectance of filter samples.

While strong correlations have been observed between filter absorption and EC concentrations (Janssen et al., 2000), the nature of this relationship may depend on the measurement location (Cyrus et al., 2003a; Brunekreef et al., 2005), and site-specific calibration of the simple absorption method is recommended.

Direct methods of EC and OC determination are available using either integrated collection on filters or semi-continuous thermal/optical carbon analyzers (e.g. the Thermal/Optical Carbon Aerosol Analyzer, Sunset Labs). The two most common analytical techniques are the IMPROVE EC/OC method and the NIOSH EC/OC method (Schauer, 2003). Methodological differences in instrument temperature and heating times result in higher EC measures by the IMPROVE method relative to the NIOSH method (Schauer, 2003; Watson et al., 2005). In addition, there is no simple relationship between measures obtained by each of these two methods; thus values obtained by either method are not directly comparable, making it difficult to compare results from studies using different analytical techniques. There is also a difficult sampling problem with gains or losses of OC while being collected on quartz filters (Chow et al., 2001). The problem is dealt with in different ways, including adding a denuder and some type of filter backup to deal with both negative and positive artifacts. These problems have affected most of the studies referenced in these sections and therefore the quantitative estimates of EC/OC concentrations in these studies carry considerable uncertainty and should be treated with caution.

14.1.6.1.1 Summary of personal exposure studies for elemental and organic carbon

Using EC as a marker, Kim D et al. (2005) identified traffic-related sources as significant determinants of personal PM_{2.5} exposures in Toronto, ON, which contributed approximately 13% to personal exposure levels. Similar findings were reported in North Carolina, where motor

vehicle exhaust contributed approximately 10% to personal PM_{2.5} exposures (Zhao et al., 2006). The specific method of thermal/optical analysis (NIOSH or IMPROVE) was not mentioned in this study, but cooking (OC marker) was identified as the largest contributor to personal PM_{2.5} exposures. Ambient levels were not reported in either study.

Noullett et al. (2006) observed strong correlations between personal PM_{2.5} absorption measures and EC concentrations among children in Prince George, using both the NIOSH ($r = 0.88$) and IMPROVE ($r = 0.92$) methods. In this study, median outdoor absorption levels exceeded personal measures, but a high correlation was detected between personal and ambient levels ($r = 0.73$). Variation was greater for personal exposure measures than for ambient levels.

The contribution of ambient PM_{2.5} and associated pollutants to corresponding personal exposures was investigated among seniors in Boston, MA, COPD patients in Baltimore, MD, and children in both cities (Koutrakis et al., 2005). EC exposures were determined using a procedure similar to the IMPROVE method of thermal/optical analysis (Chow et al., 1993). Children's EC exposures varied most, but median exposure values were generally similar for all three groups. Ambient EC levels were determined in Boston only and were similar to personal exposure levels for children and seniors monitored in this city. However, ambient EC levels explained only a small proportion of the variance in personal exposure levels.

Delfino et al. (2006) conducted a study to examine the relationship between personal and ambient air pollution and exhaled NO_x among children in Riverside and Whittier, CA. EC/OC exposures were determined using the thermal manganese dioxide oxidation technique, which generally agrees with the IMPROVE method of analysis to within $\pm 25\%$ (Fung et al. 2002). Median ambient EC levels exceeded personal exposures, while ambient OC levels exceeded personal exposures in Riverside but not in Whittier. Personal and ambient EC/OC levels were not correlated.

Moderate cross-sectional correlations were observed between personal EC exposures and home and workplace levels among school teachers in Finland ($r = 0.6$) (Toivola et al., 2004). Mean personal absorption measures were similar to workplace levels but exceeded those in the home. Outdoor measures were not reported.

Sarnat et al. (2006a) conducted a study in Steubenville, OH, to examine the impact of season and home ventilation (window opening) on the association between ambient levels and personal EC exposures in PM_{2.5}. Personal-ambient associations for EC were greater in autumn ($r = 0.66$) than in summer ($r = 0.28$), and the largest association was observed for subjects who spent some time indoors with open windows (compared with subjects who spent no time indoors with open windows). The associations were determined using a mixed model with repeated measures on the study population. On average, personal and ambient EC levels were similar and displayed similar variation, but maximum values for personal exposures exceeded maximum ambient levels. In general, these findings highlight the importance of ventilation (open windows) and season on the correlation between personal EC exposures and ambient levels.

Sørensen et al. (2005a) conducted a study in Copenhagen to investigate the extent to which outdoor concentrations influence personal exposure to PM_{2.5} and BS. In this study, personal measures varied most during colder months while ambient measures varied most during warmer months. In addition, median personal absorption measures were greater during the cold season relative to warmer months, and bedroom and front door levels were each significant predictors of personal absorption coefficients. While personal exposures were lower than values measured outside the home, they were considerably less than ambient measures collected near a busy roadway. Two studies in Amsterdam found similar results. Wichmann et al. (2005) observed higher mean personal absorbance levels in PM₁₀ samples collected from subjects living in high-traffic areas relative to low-traffic areas. Van Roosbroeck et al. (2006) reported

higher mean personal PM_{2.5} absorbance levels for children living near busy roads relative to children living at background locations.

Wu et al. (2006a) examined personal EC/OC exposures in PM_{2.5} among adult asthmatics during agricultural burning in Pullman, WA. Levoglucosan (a marker of biomass burning) levels in personal PM_{2.5} were also determined. Personal EC exposures were not significantly different during burning episodes relative to other time periods, but mean OC exposures were higher during burning periods (10.2 µg/m³) than during non-burning ones (7.7 µg/m³). As expected, levoglucosan levels in personal PM_{2.5} measures were also greater during burning episodes (0.026 µg/m³) than at other periods (0.010 µg/m³).

Jansen et al. (2005) measured personal EC exposures in PM₁₀ among elderly asthmatic/COPD subjects in Seattle, WA. Personal EC exposure levels were slightly lower than ambient values, but each 1 µg/m³ increase in personal EC exposure was associated with a significant increase in exhaled nitric oxide (NO), a marker of airway inflammation.

Few Canadian studies have examined personal EC/OC exposures to date. However, studies conducted in Toronto (Kim D et al., 2005) and Prince George (Noullett et al., 2006) each observed lower personal EC exposures than those reported for other geographic locations. Outdoor sources such as vehicle traffic appear to be an important determinant of personal EC exposures, and EC appears to be a better marker of vehicle traffic than PM_{2.5} (Cyrys et al., 2003a; Wichmann et al., 2005; Van Roosbroeck et al., 2006). The relationship between personal and ambient EC levels may depend on factors such as season, home ventilation, and location, and as a result site-specific calibration of the simple absorption method is recommended. The lack of standardized methods makes between-study comparisons difficult, however, and limited data are available to determine if specific subgroups have higher exposures. While few studies report OC levels in personal PM exposure samples, some evidence suggests that agricultural burning smoke may increase this type of exposure (Wu et al., 2006a).

14.1.6.2 Trace Elements and Ions

In the ambient environment, transition metals associated with PM originate primarily from industrial sources and traffic emissions. However, crustal materials, wood burning, and indoor sources such as cooking and smoking also contribute to elements such as calcium (Ca), silicon (Si), potassium (K), iron (Fe), and manganese (Mn) being present in PM (Larson et al., 2004; Kim D et al., 2005; See and Balasubramanian, 2006; Zhao et al., 2006). Sulphate and nitrate ions in PM are formed from the oxidation of sulphur and nitrogen oxides produced in the ambient environment by fuel combustion and industrial sources. Sulphate in particular has few indoor sources, making it a useful marker of exposure to ambient PM in personal samples (Clayton et al., 1993; Wilson et al., 2000; Sarnat et al., 2002). In general, crustal elements such as Si, aluminum (Al), Ca, Fe, magnesium (Mg), and titanium (Ti) are predominant in coarse PM, whereas K, SO₄²⁻, vanadium (V), chromium (Cr), nickel (Ni), copper (Cu), zinc (Zn), cadmium (Cd), tin (Sn), lead (Pb), arsenic (As) and selenium (Se) are more abundant in fine PM (Janssen et al., 1999b; Wang et al., 2006). In addition, some findings suggest that sulphur and Fe are the most abundant elements in ultrafine PM (Cyrys et al., 2003b). The presence of atmospheric acidic aerosols, particle strong acidity (H⁺) in particular, is due almost entirely to the presence of sulphuric acid (H₂SO₄) or ammonium bisulphate (NH₄HSO₄). Consequently, the acidity of atmospheric PM depends on both the amount of sulphur dioxide (SO₂) that is oxidized to sulphur trioxide (SO₃) and later forms H₂SO₄ as well as the amount of ammonia available to react with the sulphuric acid (US EPA, 2004). H⁺ is abundant in accumulation-mode particles and does not appear to be a useful marker of exposure to ambient PM in personal samplers, due to its greater reactivity (Brauer et al., 1989; Suh et al., 1992; Stieb et al., 1998). NH₄⁺

originates secondarily from emissions of ammonia (NH₃) from wild animals, from animal husbandry, sewage and fertilized land (US EPA, 2004).

Low particle mass concentrations in personal breathing air samples can make quantitative determination of trace elements difficult, and the destructive nature of some analytical methods often prevents multiple analyses on individual samples, despite the fact that all methods are not equally effective for all elements. Common analytical methods for trace elements and ions in PM include the following: high-resolution inductively coupled particle mass spectrometry (HR-ICP-MS), instrumental neutron activation analysis (INAA), energy dispersive X-ray fluorescence spectrometry (ED-XRF), ion chromatography (IC), flame atomic absorption spectrometry (FAAS), particle-induced X-ray emission (PIXE), and inductively coupled plasma atomic emission spectroscopy (ICP-AES). Of these methods, FAAS, HR-ICP-MS, IC, and ICP-AES are used to detect trace metals/ions in solution while ED-XRF, PIXE, and INAA are applied directly to the sample filter.

14.1.6.2.1 Summary of personal exposure studies for trace elements and ionic compounds

Kim D et al. (2005) compared the relative contribution of regional sources (SO₄²⁻ marker), traffic-related combustion sources (EC marker), and crustal materials (Ca marker) to personal PM_{2.5} exposures in Toronto, ON. Of the elements and ions analyzed, sulphate was present in the highest concentrations and displayed the most between-subject variability. However, a large portion of personal PM_{2.5} exposure could not be explained by the sources examined, and the authors speculated that indoor sources and/or subject activities also influence personal exposure levels. Ambient element concentrations in PM_{2.5} were not reported. Ebel et al. (2000) examined the correlation between personal and ambient sulphate levels in PM_{2.5} samples from Vancouver, BC. Ambient levels were slightly greater than personal exposures but the two were highly correlated (r = 0.96).

A number of additional studies have examined personal sulphate exposures as well as the correlation between personal and ambient SO₄²⁻/S levels. In these studies, median exposures and personal–ambient correlations (r) range from 0.48 to 10.6 µg/m³ and from 0.48 to 0.95 respectively, with exposures and correlations during warmer months generally exceeding those during colder months (Suh et al., 1992; Brauer et al., 2000; Hidy et al., 2000; Oglesby et al., 2000; Sarnat et al., 2000; Landis et al., 2001; Wallace et al., 2003b; Brunekreef et al., 2005; Koutrakis et al., 2005; Molnar et al., 2005; Wallace and Williams, 2005; Sarnat et al., 2006b). In addition, ambient sulphate levels generally exceed personal measures (Suh et al., 1992; Hidy et al., 2000; Oglesby et al., 2000; Sarnat et al., 2000; Landis et al., 2001; Wallace et al., 2003b; Brunekreef et al., 2005; Koutrakis et al., 2005; Molnar et al., 2005; Wallace and Williams, 2005; Sarnat et al., 2006b), but some studies have observed higher values for personal measures (Brauer et al., 2000). In general, evidence supports the use of personal sulphate as a surrogate measure of exposure to PM of ambient origin.

In Basel, Switzerland, Oglesby et al. (2000) observed personal–ambient correlations of 0.53, 0.21, 0.33, and 0.12 for Pb, bromine (Br), K, and Ca in PM_{2.5}, respectively, compared with 0.74 observed for S. Median personal exposure levels were greatest for sulphur followed by K, Ca, Pb and Br, and median personal exposures exceeded ambient levels for all elements except S. In general, findings from this study suggest that fixed-site measures are better surrogates for regional air pollution (S marker) than for traffic-related exposures (Pb and Br markers) or crustal materials (Ca marker).

A study was conducted in Toronto to investigate the potential contribution of the gasoline additive MMT to personal Mn exposures in PM_{2.5} (Pellizzari et al., 1998, 1999). Median personal

exposures for Al, Ca, and Mg in PM_{2.5} exceeded outdoor levels. Moderate cross-sectional correlations were observed between personal Mn exposures and indoor ($r = 0.56$) as well as outdoor ($r = 0.48$) levels, but fixed-site ambient monitors displayed little correlation with personal measures (Pellizzari et al., 1998). Indoor Mn levels varied less than personal and outdoor measures. Median Mn exposures in PM_{2.5} were greatest for smokers (9.2 ng/m³), metal-workers (12 ng/m³), and subway riders (12 ng/m³); the authors concluded that the majority of personal Mn exposures were from non-MMT sources—smoking, subway use, and occupational exposures (Crump, 2000). Elevated Mn exposures in PM_{2.5} were also reported for office workers in London, England, who rode the subway relative to taxi drivers who did not (Pfeifer et al., 1999), and time spent on the subway has been associated with elevated Mn, Fe and Cr in personal PM_{2.5} samples in New York City (Chillrud et al., 2004).

In a related study, Pellizzari et al. (2001) explored indoor, outdoor, and personal Mn exposures in PM_{2.5} among subjects in Indianapolis, IN. PM_{2.5} levels were generally greater than those observed in Toronto, but median personal, indoor, and outdoor Mn concentrations in PM_{2.5} were considerably less (Pellizzari et al., 2001). Similarly to what was observed in Toronto, low-to-moderate cross-sectional correlations were detected between personal Mn exposures and indoor ($r = 0.64$) and outdoor ($r = 0.39$) levels, and fixed-site measures displayed little correlation with personal measures. The authors concluded that fixed-site measures are poor predictors of personal Mn exposures and suggested that there may be a greater contribution of Mn from combustion sources in Toronto than in Indianapolis, where it was not used as a gasoline additive.

Sørensen et al. (2005b) measured transition metals in personal PM_{2.5} samples collected from students in Copenhagen, Denmark. V, Cr, platinum (Pt), Ni, Cu, and Fe were examined, and while Fe was the most abundant element in personal samples, V and Cr were each associated with oxidative DNA damage.

Magari et al. (2002) conducted a panel study in Quincy, MA, to examine the effects of PM_{2.5} metal content on HRV among construction workers. In this study, median exposures were greatest for Mn, followed by Cu, Ni, Cr, Pb, and V.

Brunekreff et al (2005) compared the median Spearman correlation coefficients (R) for different elements to the coefficients observed for PM_{2.5} mass for groups of 37 cardiovascular patients in Amsterdam, the Netherlands, and 47 in Helsinki, Finland. Sulphur in both cities, and Zn in Amsterdam only, had the R between personal–outdoor and indoor–outdoor concentrations higher than the same correlation for PM_{2.5} mass. Zn and Si in Helsinki and Fe, Ni, Mn and V in both cities had median R similar to those observed for PM_{2.5} mass, while Si in Amsterdam and K, Ca, Cu and Cl in both cities had lower R than those for PM_{2.5} mass. The high correlation can be explained by fewer indoor sources and (for sulphur) smaller spatial variation of outdoor air pollution.

Results of the Stieb et al. (1998) study showed that mean personal SO₄²⁻ was lower and less variable than the mean ambient SO₄²⁻ level. Similarly, the mean personal H⁺ was lower than the mean ambient level. There was high correlation between mean personal and fixed site SO₄²⁻ ($R^2 = 0.90$; $p < 0.0001$) and high daily concentrations measured at fixed site were reflected in high mean personal concentrations. There was little correlation between mean personal and fixed site H⁺ measurements ($R^2 = 0.13$; $p = 0.11$), although some high personal measurements corresponded to high fixed site levels.

In a study by Suh et al. (1992), for both SO₄²⁻ and H⁺, personal exposures were lower than outdoor and higher than indoor levels, while indoor levels were lower than the corresponding outdoors. The differences were greater for H⁺, which suggests that a large fraction of H⁺ is neutralized by NH₃ present inside homes. Personal H⁺ showed a substantial interpersonal

variability that could not be explained by variation in outdoor concentrations. Similar results were found by Brauer et al. (1990), Suh et al. (1993a, 1993b), and Leaderer et al. (1999). Personal NH_4^+ and NO_3^+ were higher than indoor or outdoor levels. Indoor NH_4^+ was higher than outdoor levels (Suh et al. 1992; Liang and Waldman, 1992; US EPA, 2004). Indoor NO_3^- levels do not exceed typically those outdoors (Brauer et al., 1991; Sarnat et al., 2000).

A number of studies have reported elevated trace element concentrations in personal PM samples relative to indoor and outdoor levels. In the PTEAM study of 178 residents of Riverside, CA, Özkaynak et al. (1996) observed increases ranging from 4% to 111% for a suite of 15 trace elements in personal PM_{10} samples relative to the combined average of indoor and outdoor concentrations. All elements were analyzed by ED-XRF with sulphur the only element for which the average of indoor and ambient concentrations exceeded personal exposure levels. Similar patterns have been observed in Oxford, England (Lai et al., 2004), and Goteborg, Sweden (Molnar et al., 2006), as well as in New York City and Los Angeles (Kinney et al., 2002; Sax et al., 2006). Ultimately, the relationship between trace metal concentrations in personal, indoor, and outdoor PM samples depends on indoor sources such as wood stoves, smoking, cooking, and cleaning as well as proximity to traffic or industrial areas, which may increase personal exposures to trace elements (Molnar et al., 2005).

In general, studies of trace elements and ions in personal PM exposure samples suggest that personal–ambient associations are greatest for sulphate, owing to the absence of indoor sources, and that personal exposures to elements other than sulphur often exceed indoor and outdoor levels, presumably because of the higher overall PM mass frequently found in personal exposure samples. Personal exposures to SO_4^{2-} and H^+ tend to be lower than corresponding outdoor and higher than indoor levels, while indoor levels tend to be lower than the corresponding outdoors, with differences being greater for H^+ , which suggests that a large fraction of H^+ is neutralized by NH_3 present inside homes. Personal NH_4^+ and NO_3^+ are higher than indoor or outdoor levels. Indoor NH_4^+ levels exceed the corresponding outdoors, while indoor NO_3^- levels do not typically exceed the outdoor levels. For sulphate specifically, exposures tend to be greater during the warmer months when infiltration rates and AERs are highest. Time spent on the subway appears to be an important determinant of Mn levels in personal PM samples. However, the small number of studies conducted to date makes it difficult to determine whether specific population subgroups have different exposures to various elements/ions. In addition, the current lack of standardized methods often limits between-study comparisons of exposure.

14.1.6.3 Polycyclic Aromatic Hydrocarbons

PAHs are compounds made up of two or more fused aromatic rings and are produced during the incomplete combustion of organic materials such as vehicle fuel and wood for residential heating (Sørensen et al., 2003c; Kocbach et al., 2006). PAHs are present in both gas and particle phases (Su et al., 2006), and particulate PAHs are generally present in the fine and ultrafine fractions of PM (Zielinska et al., 2004; Yang HH et al., 2005; Wu et al., 2006b). Indoor sources include incense, smoking, candle burning and cooking (Wallace, 2000; Ohura et al., 2004), but vapour phase PAHs are not reflected in PAH measures from personal PM exposure samples.

Gas chromatography (GC) and high-performance liquid chromatography (HPLC) are commonly used to characterize PAHs in personal PM exposure samples, but GC is the preferred method owing to its greater sensitivity, selectivity, and resolution (Poster et al., 2006). A number of different PAHs may be present in personal PM exposure samples, but total PAH content is often reported by adding individual PAH concentrations. The number and specific selection of individual PAHs differs between studies, and the authors often just briefly discuss or fail to

mention how they handle non-detectable species when calculating the sum; hence "total PAHs" are generally not equivalently defined across studies.

14.1.6.3.1 Summary of personal exposure studies for polycyclic aromatic hydrocarbons

No published Canadian studies were found that characterized the PAH content of personal PM exposure samples.

Miller et al. (2004) conducted a study among pregnant women in New York City and reported total PAH exposures in PM_{2.5} as the sum of eight individual compounds: benz(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(ghi)perylene, benzo(a)pyrene, chrysene/isochrysene, dibenz(a,h)anthracene, and indeno(1,2,3)pyrene. Ambient PAH levels were not reported, but in general higher exposures were observed during the heating season relative to the warmer months.

In a second study of pregnant women in New York City, Tonne et al. (2004) examined predictors of personal PAH levels in PM_{2.5}. With the addition of pyrene, the PAHs examined in this study were the same as those assessed by Miller et al. (2004). Pyrene was responsible for the majority of the total PAH mass concentration, and personal PAH exposures were associated with time spent outdoors, residential heating (time heat was on vs. time heat was off), and indoor incense burning. However, these factors explained only a small fraction of the variation in PAH exposures ($0.03 < R^2 < 0.23$). Ambient PAH levels were not reported, but an earlier investigation also observed higher personal PAH levels (benzo(a)pyrene) in PM₁₀ during the winter relative to the summer months (Waldman et al., 1991).

Zmirou et al. (2000) examined personal PAH exposures in PM_{2.5} among adults in Grenoble, France. Nine different PAHs were determined: benzo(a)pyrene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, indeno(1,2,3-c,d)pyrene, benzo(ghi)perylene, chrysene, fluoranthene, and pyrene. In general, PAH levels were 3 to 25 times greater during the winter relative to the summer months. With the exception of indeno(1,2,3-c,d)pyrene, PAH levels in ambient PM_{2.5} samples collected close to traffic emissions exceeded personal measures.

A study was conducted among adults in Taichung, Taiwan, to examine personal exposures to total PAHs in PM₁₀ (Kuo et al., 2003). Scripted activities were performed and 22 PAHs were analyzed: naphthalene, acenaphthylene, acenaphthene, fluorene, phenanthrene, anthracene, fluoranthene, pyrene, benzo(c)phenanthrene, benzo(b)naph(2,1-d)thiophene, cyclopenta(cd)pyrene, benz(a)anthracene, chrysene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(e)pyrene, benzo(a)pyrene, indeno(1,2,3-cd)pyrene, dibenz(ah)anthracene, benzo(ghi)perylene, anthanthrene, and coronene. Exposures were reported as the sum of these compounds. Mean personal exposures were highest for activities associated with charcoal burning, followed by motor vehicle exhaust and home incense burning.

Binková et al. (1995) evaluated personal PAH exposures in smoking and non-smoking women in Teplice, Czech Republic. Eight PAHs were analyzed (chrysene, benzo(a)anthracene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, dibenzo(a,h)anthracene, indeno(1,2,3-c,d)pyrene, benzo(g,h,i)perylene) and mean total PAH exposures in PM_{2.5} were similar for smokers and non-smokers. Ambient PAH levels were not reported.

Personal exposures to PAHs in PM_{3.5} were examined in Zagreb, Croatia (Šišović et al., 1996). Seven PAHs were determined (fluoranthene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, benzo(b)chrysene, benzo(ghi)perylene, and anthanthrene) and in general mean personal PAH exposures tended to be much higher during the winter months. During the winter months, outdoor concentrations for all PAHs exceeded indoor and personal measures.

However, during the summer months personal PAH levels were slightly greater than indoor and outdoor measures.

Ohura et al. (2005) conducted a study among adults in Shizuoka, Japan, to characterize personal PAH exposures in PM_{2.5} as well as indoor and outdoor levels. Total PAHs were determined and were reported as the sum of fluoranthene, pyrene, 1-methylpyrene, triphenylene, p-terphenyl, chrysene, benz(a)anthracene, perylene, benzo(e)pyrene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(j)fluoranthene, benzo(a)pyrene, indeno(1,2,3-cd)pyrene, benzo(ghi)perylene, dibenz(a,c)anthracene, dibenz(a,h)anthracene, benzo(b)chrysene, picene, coronene, and dibenzo(a,e)pyrene. Median personal exposures to total PAHs in PM_{2.5} were similar for the summer and winter months, but median living room, bedroom, workplace, and outdoor PAH levels tended to be greatest during the winter months. In this study, living room ($r = 0.57$) and bedroom ($r = 0.60$) PAH levels were significantly correlated with personal exposures during winter and summer combined.

Georgiadis et al. (2001) conducted a study in Athens and Halkida, Greece, to characterize personal PAH exposures and to explore determinants of such exposures. Total PAHs in PM_{2.5} were reported as the sum of benzo(a)anthracene, chrysene, benzo(b)fluoranthene, benzo(k)fluoranthene, benzo(a)pyrene, benzo(a,h)anthracene, benzo(ghi)perylene, and indeno(1,2,3-c,d)pyrene. Mean total PAH levels were greater during winter than in summer and total PAH exposures were associated with ETS exposure during winter. Strong to moderate cross-sectional (pooled) correlations were detected between total PAH and mass concentrations of personal PM_{2.5} ranging from 0.56 (summer) to 0.66 (winter) in Athens and 0.57 (summer) to 0.78 (winter) in Halkida. Correlations between individual PAHs and PM_{2.5} were generally greater during the winter months, with benzo(a)pyrene and chrysene displaying the highest correlations and benzo(ghi)perylene the lowest. Ambient PM_{2.5} and PAH levels were not reported.

While Canadian studies have yet to explore the PAH content of personal PM exposures, other studies have identified outdoor sources, including vehicle exhaust and charcoal burning, and indoor sources, including incense burning and ETS, as important sources of PAH exposure. In addition, current evidence suggests that PAH exposures tend to be greater during the winter months relative to warmer time-periods. However, it is difficult to compare exposures between studies owing to methodological differences, and limited data are currently available to determine if particular subgroups are more exposed to particle-bound PAHs than others. In addition, it remains difficult to determine which PAHs contribute most to personal exposures, as many of the above studies report total PAH exposures instead of values for individual compounds.

14.1.7 Sources/Factors Affecting Personal Exposure to Ambient PM

14.1.7.1 Time-activity

Levels and characteristics of PM are different in various microenvironments such as outdoors, in-vehicle, at home or in public buildings. The time a person spends in each of the microenvironments, the level of PM in those microenvironments, resuspension of PM in the immediate vicinity—all these factors determine the individual's total personal exposure.

Two extensive time-activity studies have been conducted in Canada and the United States using the same methods, both in the mid-1990s. For the Canadian Human Activity Pattern Study (CHAPS) (Leech et al., 2002), data were collected from a diary recall survey of 2381 households (65% response rate) in four cities (Vancouver, Edmonton, Toronto and St. John) from 1994 to 1995. CHAPS results are presented in Table 14.1. Similarly to an earlier

population-based study of Toronto residents (Pellizzari et al., 1998), every age group spent a majority of time indoors (87–89%), most of which was spent at home. The average time spent outdoors ranged from 5.5% to 9.5% and time spent in-vehicle ranged from 3.1% to 6%. Children and youth spent more time outdoors than adults. The larger National Human Activity Pattern Survey (NHAPS) (9386 American homes; 63% response rate) in the 48 contiguous states was conducted from 1992 to 1994. Its results indicated that Americans spent an average of 87% of their time indoors (69% of total time in a residence), 5–6% in transit and 7–8% outdoors (Klepeis et al., 2001).

The time-activity patterns reported in CHAPS and NHAPS were similar. Two subtle differences were that Canadians spent more time indoors in the winter and less time indoors in the summer, and Canadians aged 11–17 years spent more time indoors at home. Both CHAPS and NHAPS were limited to one 24-h recall period per subject, which precluded an examination of intra-individual variability. Although the Canadian survey lacked rural participants, the similarity between the results of these surveys and between locations within surveys suggested that there was little variability across mean time budgets in different studies (e.g., NHAPS and CHAPS). In an earlier study, differences in time-activities were less than 2 min per person-hour for both children and adults when geographically different locations were compared (Johnson et al., 1993). Although similar smoking levels (approx. 19%) were reported in the two surveys, time in the presence of a smoker was likely overestimated in CHAPS, because a smoker was considered to be present for the total duration of time spent in a microenvironment by a respondent. While more detailed results were available from NHAPS, the similarities between these surveys were striking. People spent most of their time indoors, mostly at home (Klepeis et al., 2001; Leech et al., 2002).

Table 14.1 Results from the Canadian Human Activity Pattern Study (source: Leech et al., 2002)

Microenvironments	Percentage of time spent in each microenvironment by age group (n) (percentage of all respondents)		
	>17 (76)	11–17 (9)	<11 (15)
Indoors at home	64	67	72
Outdoors at home	1.2	1.5	2.7
School/Public Building	3.0	12.1	5.7
Bar/restaurant	8.1	6.1	8.7
Outdoors—other	2.1	0.9	0.7
Indoors—other	4.3	8.0	4.3
In vehicles	6.0	3.1	3.7
Near vehicles—outside	0.05	0.0	0.01
Office/factory	7.8	0.22	1.07
Mall/store	3.1	1.1	1.9

Panel studies are also a source of time-activity data. The only recent Canadian panel study of children was conducted in Prince George (Noullett et al., 2006). The winter timing of this study contributed to children spending, on average, 95% of their time inside (66% of total time at home). Time spent in “other indoor” locations ranged from 2% to 14% and outdoors from 1% to 7%. These patterns were similar to other healthy children’s wintertime patterns in Boston and Baltimore (Koutrakis et al., 2005). In the latter study, time spent outdoors at home or away from home was consistently greater in summer than in winter. Other studies have generally found that children spent similar or slightly less time indoors at home, compared with the CHAPS results (Liu L-JS et al., 2003; Allen et al., 2004; Wu et al., 2005b). One study of 15 boys and 5 girls found that boys spent more time outdoors than girls (average 3h 17 min/d vs. 2h 32 min/d) (Delfino et al., 2004).

Other studies have focused on adult and elderly subjects with cardiovascular or respiratory disease. In Vancouver, a group of elderly subjects with COPD spent more time indoors at home (mean 92.41% vs. 80.84%) and less time indoors away from home (mean 2.24% vs. 8.24%) than similarly aged, healthy NHAPS participants. In contrast to the annual sampling of NHAPS, the Vancouver study was only conducted in the spring and summer (Ebelt et al., 2000). Stieb et al. (1998) found that adults with cardiopulmonary disease in St. John spent more time indoors (mean 81.8% vs. 71.0%) and at home (mean 64% vs. 39.8%) and less time outdoors (mean 7.6% vs. 15.5%) during the 7a.m.–7p.m. time period, compared with the general St. John population who participated in CHAPS. In May 2002, 70 elderly subjects (35 males) with COPD from Ottawa were compared with an age-matched subgroup from CHAPS. Both groups spent similar amounts of time indoors, but subjects with COPD spent more of this time at home, and were more likely to have A/C at home (Leech and Smith-Doiron, 2006).

Like the Canadian studies, other studies in the US and Europe have also found that people with pre-existing disease spend, on average, more time indoors at home than the CHAPS or NHAPS participants (Williams et al., 2003b; Liu L-JS et al., 2003; Allen et al., 2004; Lai et al., 2004; Rojas-Bracho et al., 2004; Koutrakis et al., 2005). Results from several studies suggested that healthy elderly subjects spent more time indoors away from home than subjects with a pre-existing disease, but that the compromised subjects spent more time indoors at home, so that overall, both groups spent similar amounts of time indoors.

Several factors have been identified that may influence the results of time-activity studies, including recall window (e.g. 12 h vs. 24 h), method of survey (e.g. self-administered vs. technician-recorded), location, season and group studied (Leech and Smith-Doiron, 2006). In the recent literature, study designs allowed subjects to complete diaries electronically or on paper (≤ 24 -h recall windows), although many studies did not use probability-based subject selection, thus precluding extrapolation to larger populations.

In conclusion, studies have generally found that Canadians (and other nationalities) spend the most time indoors, especially at home. It appears that children spend more time indoors away from home whereas elderly and compromised subjects spend more time indoors at home. Time spent in transit and indoors at work or school followed a decreasing gradient across groups of adults, children and the elderly (with or without a pre-existing disease). There are few data on the time-activity patterns of adolescents, which may be an area of interest for future research.

A few studies have used continuous personal exposure PM mass data (from personal DataRAMs) and corresponding time-activity data to estimate mean exposure occurring in the different microenvironments, such as indoors at home, indoors elsewhere, in transit, at work, outdoors at and away from home. All of these studies have been carried out in the US, specifically Baltimore, MD, Fresno, CA, Seattle, WA and Alpine, CA, focusing on elderly, children (healthy and asthmatic) and persons with pre-existing disease. None of the studies looked at healthy adults.

In a study in Seattle of healthy elderly ($n = 28$), asthmatic children ($n = 19$), and elderly with COPD ($n = 24$) and CHD ($n = 27$), subjects were monitored for as many as three sessions (Allen et al., 2004). The median outdoor (at home) $PM_{2.5}$ level measured at the homes of 40 participants was $7.5 \mu\text{g}/\text{m}^3$ (Goswami et al., 2002). A subset of participants carried pDRs; time-activity and pDR data were combined over 30-min periods. Data were pooled in 30-min periods. The overall GM personal pDR level was $6.9 \mu\text{g}/\text{m}^3$ (geometric SD = 2.6); the mean level was $10.9 \mu\text{g}/\text{m}^3$ (SD = 19.1). For the elderly groups, the average percentage of time spent outdoors ranged from 2% to 3%, while the percentage of exposure received during that time ranged from 4% to 5%. The asthmatic children spent on average 7% of their time outdoors, receiving 11% of their exposure while there. For the elderly groups (healthy, COPD and CHD), the average

percentage of time spent indoors ranged from 94% to 95% (85–90% at home, 5–9% indoors elsewhere) where they received 89–90% of their total daily exposure (79–83% at home, 8–11% indoors elsewhere). For asthmatic children, the average percentage of time spent indoors was 90% (67% at home, 23% at school) where they received 84% of their exposure (50% at home, 34% at school). The percentage of time the elderly subjects spent in transit ranged from 3% to 4%, while the percentage of exposure received during that time ranged from 5% to 6%. The asthmatic children spent on average 3% of their time in transit, receiving 5% of their exposure while there.

Howard-Reed et al. (2000) carried out similar studies in Baltimore and Fresno. The Baltimore panel study included 21 elderly subjects, 5 of whom wore a pDR in conjunction with a PEM for 4–14 days between July 26 and August 22, 1998. In Fresno, 10 of 51 elderly participants wore the pDR with the PEM for 2–7 24-h periods between April 19 and May 15, 1999. The mean ambient PM_{2.5} levels during the two studies were similar; 22.0 µg/m³ in Baltimore (Williams et al., 2000d) and 21.7 µg/m³ in Fresno (Evans et al., 2000). The corresponding mean personal PM_{2.5} exposure (for the entire cohort) was 13.0 µg/m³ in Baltimore and 13.3 µg/m³ in Fresno; the mean pDR personal levels are not provided. The five participants who wore the pDR in Baltimore spent an average of 3% of their time outdoors and received 6% of their total PM exposure while outdoors. In Fresno, the 10 participants spent an average of 6% of their time outdoors and received an average 9% of their total exposure while outdoors. In Baltimore, participants spent an average of 95% of their time indoors (77% at home, 18% elsewhere), where they received 89% of their total exposure (66% at home, 23% elsewhere). In Fresno, the participants spent an average of 91% of their time indoors (72% at home, 19% elsewhere) where they received 86% of their exposure (63% at home, 23% elsewhere). In Baltimore, participants spent an average of 3% of their time and received 6% of their total PM exposure in transit. In Fresno, participants spent an average of 4% of their time and received 6% of their total exposure while in transit.

Wu et al. (2005b) monitored 20 asthmatic children from Alpine, CA, for 2 weeks during fall 1999 and spring 2000. The personal DataRAM data were adjusted to be comparable to Harvard Impactor gravimetric measurements. The average adjusted 24-h ambient pDR level was 10.8 µg/m³ (range 2.7–20.3 µg/m³), while the mean personal level was 24.2 µg/m³ (range 1.6–71.9 µg/m³). On average, the children spent a total of 14% of their time outdoors, where they received 22% of their total personal exposure. They averaged 83% of their time indoors (62% at home, 13% at school and 7% elsewhere) where they received 74% of their exposure (45% at home, 22% at school and 7% elsewhere). The children also spent a total of 3% of their time and received, on average, 5% of their total personal exposure while on the road or in transit.

The results from these studies are remarkably similar. For the elderly participants in all four locations, the lowest average exposure levels occurred while indoors at home; however, most of their daily exposure (average 86–90%) occurred while indoors either at home or elsewhere, where they spent, on average, 91–95% of their time. The asthmatic children in the Seattle study spent, on average, slightly less of their time indoors (90%), where they received 84% of their exposure. The children in Alpine also spent less time indoors (average 83%), where they received 75% of their total PM exposure. As discussed earlier, exposure while indoors will include exposure to both non-ambient PM and ambient PM that has infiltrated indoors. The elderly groups spent, on average, 2–6% of their time outdoors, where they experienced 4–9% of their PM exposure, which would be predominantly ambient PM. The asthmatic children in both studies spent more time outdoors (averaging 7% of their time in the Seattle study and 14% of their time in the Alpine study), where they received 11% and 22% of their exposure, respectively. The percentage of time spent in transit was remarkably similar across groups: the

mean ranged from 3% to 6% of time, resulting in an average of 5–6% of total personal exposure.

These studies are also useful in identifying very high short-term personal exposure peaks. For example, in the study described above, Wallace et al. (2006a) identified activities associated with short-term peaks greater than 1500 µg/m³, including cooking, smoking, grooming, cleaning, yard work and less common activities such as burning food and using a fireplace. Some short-term peaks were also associated with driving and exposure to car exhaust while loading a car. Similar activities have been associated with short-term peaks in indoor levels in other studies. These activities are generally associated with personal activities or microenvironmental exposures that provide short episodic PM excursions above a “background” level.

14.1.7.2 Personal Exposure to Ambient PM That Has Infiltrated Indoors

Ambient particles penetrate buildings through open doors and windows, cracks and crevices in the building shell and mechanical ventilation systems. Consequently, people are exposed to ambient PM that has infiltrated indoors and to PM that has been generated from indoor sources, including resuspension. It is not possible to directly measure the ambient PM that has infiltrated indoors or the ambient component of personal exposure, so a number of methods have been used to estimate these components. The infiltration factor (F_{inf}) has been defined as the proportion of ambient particles that infiltrate indoors and remain suspended. It is a function of the AER in a building, and the particle penetration efficiency and particle removal rate, both of which are dependent on particle size. The equation for F_{inf} is

$$F_{inf} = \frac{P\alpha}{\alpha + k} \quad (1)$$

where P = penetration coefficient (a number between 0 and 1 describing the fraction of particles of the size being considered that can penetrate the building envelope

α = AER, describing the rate at which outdoor air replaces indoor air, and

k = the deposition rate, the rate at which particles deposit onto surfaces.

Analogous to F_{inf} , the “outdoor personal exposure factor,” F_{pex} , is the percentage of the ambient concentration that a person receives as personal exposure (Wallace and Williams, 2005). Some authors have referred to this as α , the “personal attenuation factor” (US EPA, 2004; Wilson and Brauer, 2006), “ambient contribution factor” (Allen et al., 2004), “ambient exposure attenuation factor” (Ott et al., 2000) and “ambient exposure factor” (Wilson, pers. comm.).

In a few studies, investigators have used various methods to also estimate separately the mean ambient and non-ambient components of indoor PM levels and/or personal exposure to PM. In some cases the method used in estimating the ambient component is based on ambient PM levels from a fixed-site monitor, so that exposures that occur in outdoor microenvironments (such as traffic microenvironments) are not reflected in this “ambient” estimate, but end up in the “non-ambient” component of exposure.

14.1.7.2.1 Estimates of F_{inf} and ambient/non-ambient components of indoor levels

No published Canadian studies of the infiltration factor for any size fraction were found. The following sections summarize the estimates of F_{inf} and ambient/non-ambient contributions to indoor PM obtained from various US and European studies for PM_{2.5}, PM_{2.5–10} and PM₁₀.

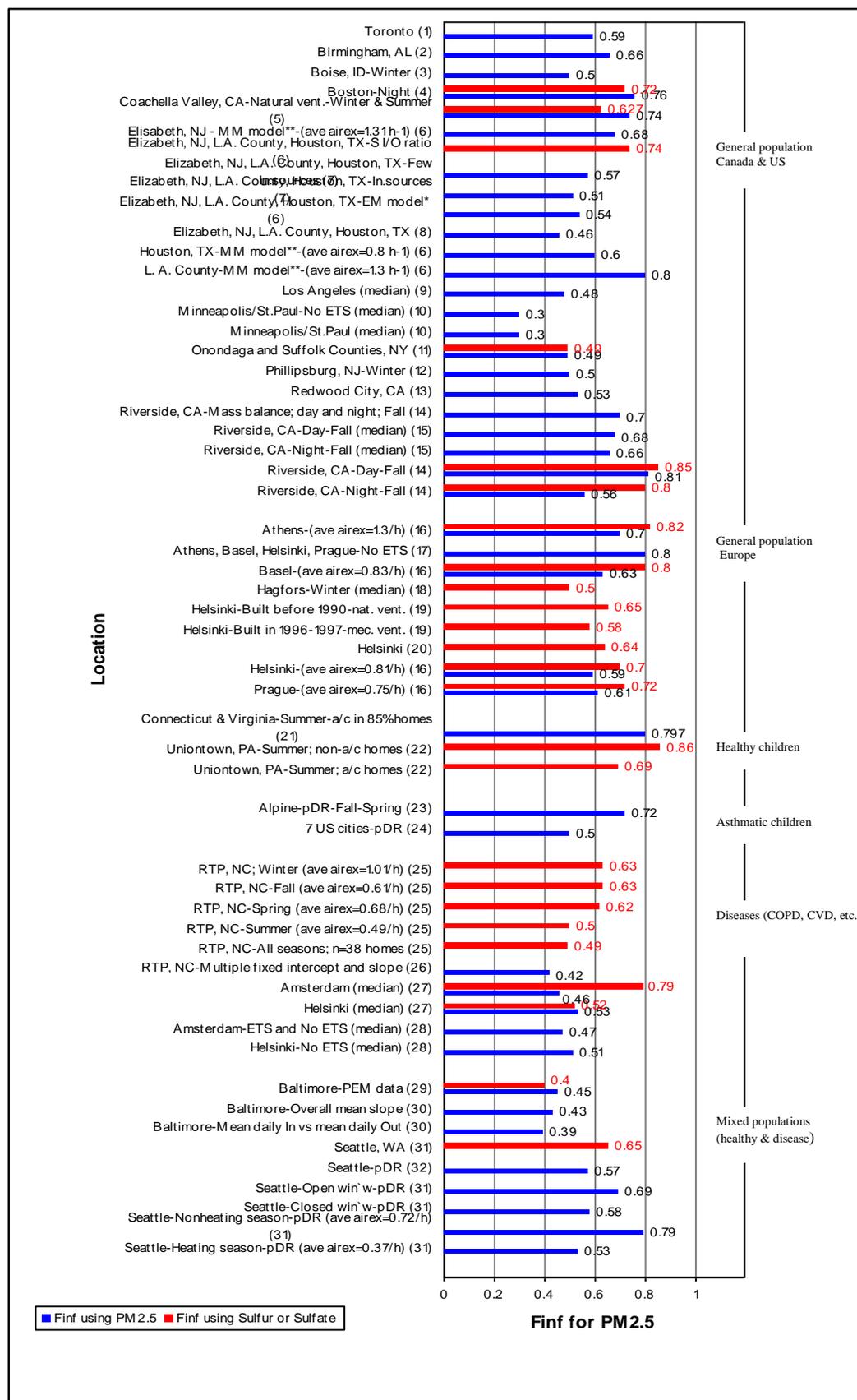
PM_{2.5}: Figure 14.5 contains a graphical summary of published mean (or median) residential F_{inf} estimates for PM_{2.5} from studies carried out in the US and Europe. The average F_{inf} ranged from 0.3 in Minneapolis/St. Paul (Adgate et al., 2003) to 0.82 in Athens (Hänninen et al., 2004) and

Riverside (Özkaynak et al., 1996a). F_{inf} estimates, based on $PM_{2.5}$ measurements (e.g. $PM_{2.5}$ indoor/outdoor (I/O) regressions or ratios), are given in blue, estimates based on sulphur or SO_4^{2-} measures are given in red (many studies provide both estimates). Fewer studies have measured F_{inf} in individual houses (see below). Most studies that have estimated F_{inf} using both $PM_{2.5}$ and sulphur or SO_4^{2-} ratios and regressions report higher F_{inf} estimates for S/SO_4^{2-} than for $PM_{2.5}$. It should be noted that because there are indoor sources for $PM_{2.5}$ but much less so for S, estimates from $PM_{2.5}$ regressions may be more susceptible to unstable intercepts (which are estimates of the indoor source component). Hence it is likely that sulphur regressions provide more accurate estimates of F_{inf} . As well, higher F_{inf} estimates based on S/SO_4^{2-} measures are consistent with S/SO_4^{2-} being in the smaller size fraction of $PM_{2.5}$, with lower deposition rates and subsequent higher F_{inf} .

Considerable variability in median/mean F_{inf} is seen between communities; however, only the European data by Hänninen et al. (2004) have been obtained using a probability-based sampling method. All the other data are from convenience samples, making direct comparisons between communities less meaningful. Within the Seattle study (reference 19 on Figure 14. 5 (Brauer et al., 1989)), the authors reported higher infiltration rates during periods of open window use and in the non-heating season. The low values of about 0.4 observed for the Baltimore retirement-home study are consistent with the likelihood that the building filtered and recirculated much of the ventilation air. These determinants will be discussed in more detail in Section 14.1.7.2.3.

In most cases, the estimates in Figure 14.5 are mean estimates across all homes measured in each study. A few studies have measured F_{inf} s in individual homes; in these cases, considerable between-home variability in F_{inf} was reported (Lachenmyer and Hidy, 2000; Williams et al., 2000a, 2000b, 2000c; Adgate et al., 2003; Allen et al., 2003; Wu et al., 2005b; Wallace et al., 2006b; Sarnat et al., 2006b). For example, Wallace et al. (2006b) estimated the $PM_{2.5}$ infiltration factor based on sulphur indoor/outdoor ratios from 36 homes in the Research Triangle Park, NC, area during four seasons in 2000–2001, 7 d per season. The mean individual F_{inf} across homes ranged between 0.26 and 0.87 with higher values in the winter (mean = 0.63; AER of 1.01/h; n = 223 matched indoor–outdoor samples) than in the summer (mean = 0.5; AER of 0.48/h; n = 179 matched indoor–outdoor samples), which is a reversal of the normal pattern in other northern US cities (Long et al., 2001a; Sarnat et al., 2002; Allen et al., 2003). The lower F_{inf} levels in the summer are probably due to the use of A/C systems (with closed windows and doors). Sarnat et al. (2002) reported the nighttime I/O ratios for a subset of six Boston homes (46 sampling days) from a study by Long et al. (2000) carried out in 1998. The mean $PM_{2.5}$ ratio was 0.76 but ranged from 0.41 to 1.11, while the mean sulphur ratio was 0.72, ranging from 0.33 to 1.07. Estimates greater than one indicate possible $PM_{2.5}$ and sulphur sources during the nighttime. Adgate et al. (2003) reported individual, longitudinal indoor–ambient $PM_{2.5}$ regression slopes (based on 7–15 d of sampling data per person), ranging from -0.75 to 2.1 for days without tobacco or occupational PM exposure (median 0.30; n = 22 measurements for 9 monitored days) in a group of 32 healthy non-smoking adults in Minneapolis/St. Paul, MN. Sampling was carried out during the spring, fall and winter of 1999. Williams et al. (2000a, 2000b, 2000c) reported a range of longitudinal, individual indoor–outdoor $PM_{2.5}$ regression slopes of 0.22–0.79 (mean 0.43; n = 220 apartment samples) (based on up to 23 days of sampling data per person) in a study of 21 healthy elderly and elderly with COPD and CVD in Baltimore during July to August 1998. Brunekreef et al. (2005) reported a range of individual indoor–ambient regression slopes for non-ETS-exposed participants from Amsterdam of 0.04–1.08 (median 0.47; n = 31 homes) and a range of slopes for Helsinki participants of 0.02–2.73 (median 0.51; n = 46 homes) (based on 3–13 d of sampling data per person). In a study of healthy elderly, elderly with COPD or CHD, and children with asthma in Seattle (October 1999

Figure 14.5 Mean residential PM_{2.5} F_{inf} from various studies



References for Figure 14.5:

- (1) Pellizzari et al. (1998)—Pooled PM_{2.5} regression
- (2) Lachenmyer and Hidy (2000)—Estimated AER from blower door test, then estimated F_{inf} from AER using curves from Wilson and Suh (1997) (based on PTEAM data)
- (3) Lewis (1991)—*Mass balance model and I-O regression
- (4) Sarnat et al. (2002)—PM_{2.5} I/O ratios and sulphur I/O ratios
- (5) Geller et al. (2002)—I-O regression
- (6) Meng et al. (2005b) RIOPA study—Sulphur I/O ratio and *3) External mixture model (overall)—weighted mean of the F_{inf}s of the PM_{2.5} components and **4) Microscopic mixture model (overall)—Robust regression of I-O mean PM component values
- (7) Reff et al. (2005)—PM_{2.5} I-O regression
- (8) Meng et al. (2005a) (JEAE)
- Weisel et al. (2005)—1) Mass balance model (nonlinear regression single $P, k; F_{inf}=\alpha*P/(\alpha+k)$) and 2) RCS (I-O regression over all homes)
- (9) Sarnat et al. (2006b)—I/O ratios
- (10) Adgate et al. (2003)—Longitudinal I-A regression
- (11) Koutrakis and Briggs (1992)—I-O regression
- (12) Liou et al. (1990)—I-A regression
- (13) Kopperud et al. (2004)—Indoor-outdoor air exchange model (I/O model) and chemical mass balance model (CMB)
- (14) Özkaynak et al. (1996a)—PM_{2.5} I-O regression (Özkaynak et al., 1996a) and sulphur I-O regression (Özkaynak et al., 1996a) and mass balance model (Özkaynak et al., 1996b)
- (15) Wilson and Suh (1997)— $P*\alpha/(\alpha+k)$, with P, k estimates from PTEAM
- (16) Hänninen et al. (2004)—Based on sulphur measurements (Estimated corrected for PM_{2.5} using ratio of regression coefficients)
- (17) Kousa et al. (2002)—Log linear I-A regression
- (18) Molnar et al. (2005)—Sulphur I/O ratio
- (19) Hänninen et al. (2005b)—Based on sulphur measurements I-O regression (slopes—corrected for PM_{2.5} using ratio of regression coefficients)
- (20) Hänninen et al. (2005a)—Based on sulphur measurements I-O regression (slopes—corrected for PM_{2.5} using ratio of regression coefficients)
- (21) Leaderer et al. (1999)—I-O regression 40 homes
- (22) Suh et al. (1992)—Sulphate I/O ratio S/SO₄²⁻ data
- (23) Wu et al. (2005b)—Recursive model with continuous PM data (pDR1000)
- (24) Wallace et al. (2003a)—I-O regression overall seven cities (New York, Boston, Chicago, Dallas, Seattle, Tucson); pDR is adjusted to FRM monitor like Wu et al. (2005b)
- (25) Wallace et al. (2006b)—Sulphur I/O ratio and individual home sulphur I-O regression
- (26) Williams et al. (2003b)—Mixed models
- (27) Janssen et al. (2005)—PM_{2.5} individual I-A regression and sulphur individual I-A regression
- (28) Brunekreef et al. (2005)—1) PM_{2.5} individual I-A regression
- (29) Landis et al. (2001)—3) Linear mixed I-O regression (PEM data) and SO₄²⁻ linear mixed I-O regression (PEM data)
- (30) Williams et al. (2000c) (Part. I)—Individual I-O regression
- (31) Allen et al. (2003)—Recursive model with continuous PM data
- (32) Liu L-JS et al. (2003)—Recursive model with continuous PM data

Notes:

*3) External mixture model (overall)—weighted mean of the F_{inf}s of the PM_{2.5} components

**4) Microscopic mixture model (overall)—Robust regression of I-O mean PM component values

to March 2002), Allen et al. (2003) used a recursive model with continuous PM data to estimate individual F_{inf} values, ranging from 0.24 to 1.00 (median 0.61, mean 0.65; 44 residences; $n = 55$ all monitoring events).

A limited number of studies have provided estimates of mean ambient and non-ambient contributions to indoor $PM_{2.5}$ levels (Figure 14.6; Lewis, 1991; Allen et al., 2003; Hänninen et al., 2004; Meng et al., 2005b; Wallace et al., 2006a, 2006b). Estimates from other studies that are contained in the figure have been calculated using the mean F_{inf} , mean outdoor/ambient PM concentration and mean indoor PM concentration. As discussed earlier, F_{inf} estimates based on PM indoor–outdoor regression are not as accurate as those based on S/SO_4^{2-} measures, so the additional ambient/non-ambient component estimates have only been calculated where the F_{inf} has been based on S/SO_4^{2-} measures. In almost all cases, the mean ambient component is equal to or higher than the corresponding mean non-ambient (indoor) component, highlighting the importance of infiltration of ambient PM to indoor environments.

Only a couple of studies have provided the range of estimates of the ambient and non-ambient components across individual homes (Allen et al., 2003; Wallace et al., 2006a, 2006b). Wallace et al. (2006b) estimated the components for individual homes in four seasons in a study of 37 CVD patients in Research Triangle Park using I/O ratios of sulphur as estimates of F_{inf} . As seen in Figure 14.6, there was a considerable range of both the ambient and non-ambient components across homes.

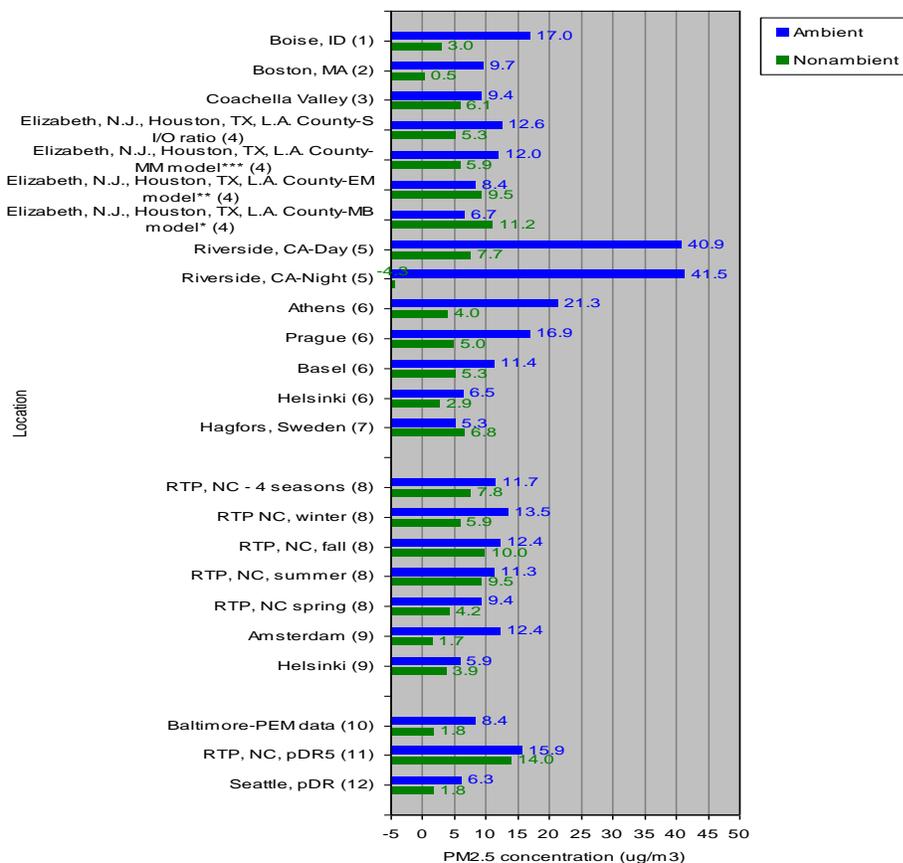
PM_{10-2.5}: Three US studies have estimated F_{inf} for the coarse size fraction ($PM_{10-2.5}$). Long et al. (2001a) reported a mean $PM_{10-2.5}$ F_{inf} of 0.28 in Boston, MA, from a survey of nine homes, compared with a mean $PM_{2.5}$ F_{inf} of 0.74 from the same homes. Geller et al. (2002) found a mean F_{inf} of 0.3 in a study of 13 homes in Coachella Valley (desert), CA, compared with a mean of 0.74 for the $PM_{2.5}$ F_{inf} for the same homes. In a study of Riverside, CA, homes in fall 1990, the median F_{inf} for coarse particles was 0.49 in the day and 0.46 in the night; both levels were lower than the median F_{inf} for $PM_{2.5}$ particles of 0.68 in the day and 0.66 in the night (Wilson and Suh, 1997). No European studies were identified. These few studies indicate that infiltration of coarse PM is lower than $PM_{2.5}$; the effect of particle size on F_{inf} is discussed in more detail in Section 14.1.7.2.3.

PM₁₀: Five US studies and one European study estimated the PM_{10} infiltration factor. The mean estimated PM_{10} F_{inf} ranged from 0.22 in Los Angeles, CA (Linn et al., 1999) to 0.5 in Phillipsburg, NJ (Lioy et al., 1990) and 0.6 in Riverside, CA (Özkaynak et al., 1996b, cited in US EPA, 2004). A median PM_{10} F_{inf} of 0.47 was measured in the households of 37 non-smoking adults 50–70 years old in Amsterdam, the Netherlands, in 1994 (Janssen et al., 1998). Ott et al. (2000) used the slope of the indoor–outdoor regression equation to estimate a F_{inf} of 0.55 for the Phillipsburg data set.

Ultrafine PM: Infiltration data for UFPs are limited, but it appears that F_{inf} is smaller for UFPs and increases with increasing particle size through the 0.01–0.1 μm size fraction. For example, Sarnat et al. (2002) estimated the UFP infiltration factors in six occupied non-smoking homes in Boston, MA, in 1998 (subset of data from Long et al., 2001a). F_{inf} was estimated as the I/O ratio during nighttime (non-source) period for 46 sampling days. The mean F_{inf} showed a slight increase from 0.57 to 0.71 across the size categories from 0.02 to 0.1 μm .

Long et al. (2001a) found similar results based on mass balance equations of data from nine homes in the same study. Zhu et al. (2005) estimated F_{inf} by measuring I/O ratios of PNs in four two-bedroom apartments in Los Angeles, CA, from December 2003 to January 2004 under different ventilation conditions and during periods without indoor PM sources. AERs ranged from 0.31 to 1.11/h, although estimation of AERs in apartments is difficult. Some of the tracer

Figure 14.6 Mean ambient and non-ambient components of indoor PM_{2.5} from various studies



References for Figure 14.6:

- (1) Lewis (1991)—mass balance
- (2) Sarnat et al. (2002)—Sulphur I/O ratio
- (3) Geller et al. (2002)—Sulphur I-O regression
- (4) Meng et al. (2005b)—Sulphur I/O ratios
- (4) Meng et al. (2005b)—4 Microscopic mixture model (overall)—Robust regression of I/O mean PM component values
- (4) Meng et al. (2005b)—3 External mixture model (overall)—weighted mean of the F_{inf} s of the 2 PM_{2.5} components
- (4) Meng et al. (2005b)—2 Mass balance model (overall)
- (5) Özkaynak et al. (1996a); (EPA report); Özkaynak et al. (1996b)—Sulphur I-O regression
- (6) Hänninen et al. (2004)—Sulphur regression: mean of individual homes with adjustment by $F_{inf}PM_{2.5}/F_{inf}Sulphur$
- (7) Molnar et al. (2005)—Sulphur I/O ratio
- (8) Wallace et al. (2006b)—Sulphur I/O* C_{out} for individual homes
- (9) Janssen et al. (2005)—Sulphur individual—regression
- (10) Landis et al. (2001)—Sulphur I-O regression
- (11) Wallace et al. (2006a) (pDR)—average of individual means/remove peaks
- (12) Allen et al. (2003) (pDR)—recursive model

gas may go into the adjacent parts of the building, which would lead to overestimation of the air exchange. The estimated F_{inf} s for particles in the size range 10–20 nm were considerably lower (0.1–0.4) than for the 70–100 nm size fraction (0.6–0.9).

In a study of 17 non-smoking households in the Los Angeles area, Sarnat et al. (2006b) calculated the indoor/outdoor concentration ratios during overnight (no indoor sources) to estimate the infiltration factor for UFPs in the 0.02–10 μm size ranges. The median F_{inf} increased from around 0.5 for the smallest particles (0.02 μm) to a maximum of 0.65–0.8 for particles around 0.2–0.3 μm . For particle size categories greater than 0.3 μm , F_{inf} s decreased with increasing particle size to values less than 0.17 for the largest particle sizes (5–10 μm).

Hussein et al. (2005) estimated a mean F_{inf} of 0.34 (SD = 0.11) in five unoccupied non-smoking homes in Espoo, Finland, in February 2001 (based on mean I/O ratio). Hämeri et al. (2004) measured indoor/outdoor ratios of UFPs in one home in Friisilä, Finland. I/O ratios were lowest for nucleation mode particles (particle diameter 8–25 nm; mean I/O ratio about 0.25), and similar for Aitken mode (particle diameter 25–90 nm, mean I/O ratio about 0.6) and accumulation mode particles (AMPs) (particle diameter 90–400 nm, mean about 0.6).

In a study of levels of UFPs in a Helsinki, Finland, office building, the indoor PN followed the outdoor concentration with approximately a 20-min delay during the night, when the mechanical ventilation was not on (mean AER = 0.3/h). In the daytime when the ventilation was on (mean AER = 3.7/h) the delay was about 10 min (Koponen et al., 2001).

In a study during January and February 1997 of particulate levels in a classroom of an elementary school in Lindon, UT, the daytime and nighttime F_{inf} s for total PNs were identical (slope = 0.16), with the I/O correlation of 0.81 during the day and 0.88 during the night (Patterson and Eatough, 2000).

The effect of particle size on F_{inf} is discussed in more detail in Section 14.1.7.2.3.

Chemical components of PM: S/SO₄⁻², EC, elements, PAHs: Infiltration varies for particles of different chemical composition, primarily due to their different size distribution. There are limited data on infiltration factors for various PM components. A few studies have estimated the infiltration factor for EC, usually based on the slope of indoor–outdoor linear regression models. Meng et al. (2005b) estimated a mean F_{inf} of 0.59 for EC in homes in Houston, TX, Los Angeles County, CA, and Elisabeth, NJ, based on a mass-balance model. Other estimates of mean F_{inf} for EC have been made from studies in Coachella Valley, CA—0.74 (Geller et al., 2002), Baltimore, MD retirement apartments—0.52 (Landis et al., 2001), and Riverside, CA—0.59 (Na and Cocker, 2005). A study by Sarnat et al. (2006b) reported a median F_{inf} of 0.84 for BC measurements in 17 Los Angeles-area homes based on an I/O ratio during overnight non-source periods (the corresponding median PM_{2.5} F_{inf} was 0.48). A study in four European cities (EXPOLIS, Götschi et al., 2002) reported F_{inf} s for BS from a multiple regression model of 0.61, 0.86, 0.79 and 0.20, respectively for Athens, Greece, Basel, Switzerland, Helsinki, Finland, and Prague, Czech Republic. The estimate for Prague is based on 20 observations and has a large confidence interval (-0.2–0.6).

There are a limited number of studies that have estimated the infiltration factors for other PM_{2.5} components: Geller et al., 2002 (Coachella Valley); Long and Sarnat, 2004 (Boston); Janssen et al., 2005 (Amsterdam and Helsinki); Meng et al., 2005b (RIOPA). The study by Meng et al. (2005b) found generally higher F_{inf} s for elements known to be associated with the fine fraction, such as Br, Vn, Pb, Ni, As and lower F_{inf} s for coarse-mode PM elements (e.g. Ca, Si, Al) even within the PM_{2.5} size fraction, however as discussed before, the difficulty in measuring AERs in apartments and in estimating F_{inf} s for components with indoor sources may make these estimates more unreliable.

Other characteristics such as volatility (Geller et al., 2002) may affect the infiltration. For example, freeway particles have a large fraction of volatile components, especially particles below 50 nm (Kittelson, 1998). The volatile component of particles may be lost to building walls during the infiltration processes (Lunden et al., 2003a). Some of the particles in the 20–40 nm size range may lose their volatile components and become particles of 20 nm or less (Lunden et al., 2003b; Kuhn et al., 2005). Several studies have found lower infiltration rates for ammonium nitrate, attributed to its volatility. As ammonium nitrate enters the house, it undergoes transformations to gas phase ammonium (NH_3) and nitric acid (HNO_3), which are subsequently lost by deposition and sorption to indoor surfaces; HNO_3 is sorbed to the walls at faster rates than NH_3 , which appears to accumulate in the gas phase (Lunden et al., 2003a, 2003b). This volatilization is a complex function of ventilation rate, temperature and gas-phase concentrations (Lunden et al., 2003a). In a study of infiltration in 17 Los Angeles-area homes (Sarnat et al., 2006b) the authors found the lowest F_{inf} (median 0.18) for volatile NO_3^- particles, and the highest F_{inf} (median 0.84) for BC, a non-volatile species. The F_{inf} for $\text{PM}_{2.5}$ was situated between these two values (median 0.48). The authors attributed the low infiltration rate of NO_3^- particles to volatilization once indoors, in addition to depositional losses upon building entry. Further studies are needed to understand the influence of particle volatility on penetration and deposition rates (Zhu et al., 2005).

One study looked at infiltration of PAHs into 61 occupied Berlin, Germany, apartments during February–June 2000 (Fromme et al., 2004). A GRAVIKON PM_4 mobile dust sampling system was used, which had a 50% collection efficiency at 4 μm mass aerodynamic diameter and zero efficiency at 7.1 μm . PM sampling was carried out over 7–8 h, one sample per apartment. The I/O regression slope for benzo(a)pyrene was 0.81, indicating substantial infiltration of PAHs. The median indoor B(a)P concentration was 0.04 ng/m^3 (max 0.67 ng/m^3); the median outdoor concentration was 0.04 ng/m^3 (max 0.91 ng/m^3).

14.1.7.2.2 Estimates of F_{pex} and ambient/non-ambient components of personal exposure

Figure 14.7 shows mean F_{pex} and Figure 14.8 is a graph of the mean ambient and non-ambient components of exposure from all available studies of $\text{PM}_{2.5}$ in Canada, the US and Europe. Again, estimates of the non-ambient and ambient components of exposure have been calculated for studies that have provided a mean $\text{PM}_{2.5}$ F_{inf} (if based on $\text{S}/\text{SO}_4^{2-}$ measures), mean outdoor/ambient concentration and mean personal exposure level (Landis et al., 2001; Meng et al., 2005a; Koutrakis et al., 2005; Janssen et al., 2005). Estimates for PM_{10} and $\text{PM}_{10-2.5}$ are discussed in the text below.

In Canada, four $\text{PM}_{2.5}$ field studies and one modelling study have provided information regarding F_{pex} and ambient/non-ambient components of personal exposure.

$\text{PM}_{2.5}$: Three Canadian studies are available, all examining small groups of people with cardiac and/or respiratory disease. Stieb et al. (1998) reported the results of personal–ambient regression analysis for sulphate, from a study of 21 adults with cardiorespiratory disease in St. John in summer 1995. Each participant provided up to four 8-h personal exposure samples. The regression was carried out on the pooled (not individual) sulphate data; the slope of the pooled regression analysis was 0.6, an estimate of F_{pex} , indicating that on average, participants were exposed to 60% of the ambient PM concentration.

Kim D et al. (2005, 2006) measured personal and ambient $\text{PM}_{2.5}$ levels in a study of 24 cardiac patients in Toronto from August 1999 to September 2001. Participants provided eight to ten 24-h personal exposure samples over a 10-week period; the mean personal $\text{PM}_{2.5}$ exposure was 22 $\mu\text{g}/\text{m}^3$ (SD 42 $\mu\text{g}/\text{m}^3$, median 14 $\mu\text{g}/\text{m}^3$, range 4–503 $\mu\text{g}/\text{m}^3$). The mean ambient concentration was 11 $\mu\text{g}/\text{m}^3$ (SD 8 $\mu\text{g}/\text{m}^3$, median 9 $\mu\text{g}/\text{m}^3$, range 0–42 $\mu\text{g}/\text{m}^3$). Regression analysis of the personal–ambient $\text{PM}_{2.5}$ relationships was performed for each participant; the median slope, an

estimate of median F_{pex} , was 0.75 (range -0.07–1.62). This would suggest an average personal exposure to ambient PM of $0.75 \times 11 \mu\text{g}/\text{m}^3 = 8.25 \mu\text{g}/\text{m}^3$ and an average non-ambient component of $22 - 8.25 = 13.75 \mu\text{g}/\text{m}^3$.

Ebelt et al. (2005) and Wilson and Brauer (2006) report results from a study of 16 COPD patients in Vancouver between April and September 1998. Each participant provided seven 24-h personal $\text{PM}_{2.5}$ exposure samples, which were subsequently analyzed for SO_4^{2-} . Wilson and Brauer (2006) report that the pooled personal–ambient regression for $\text{PM}_{2.5}$ had a slope of 0.77, while the slope from the pooled personal–ambient SO_4^{2-} regression was 0.74; the mean pooled personal–ambient SO_4^{2-} ratio was 0.71 (0.17) (i.e. estimates of F_{pex}). These mean estimates are similar to that found in the study by Kim D et al. (2005, 2006) of cardiac patients (0.75), but, as with the Kim study, this study also reported large individual variability (range of slopes (i.e. F_{pex} : 0.09–0.99), presumably reflecting the variability between individuals in time spent outdoors and the residential building characteristics that affect infiltration of ambient PM indoors. The variability may also reflect the very small number of points (seven) in each regression, which can be unduly influenced by one of two outlying points. The daily ambient PM levels ranged from 4.2 to 28.7 $\mu\text{g}/\text{m}^3$, with a mean of 11.4 $\mu\text{g}/\text{m}^3$ (SD 4.1 $\mu\text{g}/\text{m}^3$) and the total personal $\text{PM}_{2.5}$ exposure ranged from 2.2 to 90.9 $\mu\text{g}/\text{m}^3$, with a mean of 18.5 $\mu\text{g}/\text{m}^3$ (SD 14.6 $\mu\text{g}/\text{m}^3$) (Wilson and Brauer, 2006).

Based on the F_{pex} estimated from the sulphate P/A ratio, the mean ambient component was 8.1 $\mu\text{g}/\text{m}^3$ (SD 14.6 $\mu\text{g}/\text{m}^3$; range 0.9–21.3 $\mu\text{g}/\text{m}^3$) and the mean non-ambient component was 10.4 $\mu\text{g}/\text{m}^3$ (SD 14.2, range -2.6–85.0 $\mu\text{g}/\text{m}^3$). Based on the percentile distribution (90, 75, 50, 25, 10) of the individual daily values of the measured and estimated concentration and exposure parameters, including total personal exposure ($T_{2.5}$), ambient concentration ($C_{2.5}$), ambient component of personal exposure ($A_{2.5}$) and non-ambient component of personal exposure ($N_{2.5}$), there was much more between-person variability in the non-ambient component of exposure than the ambient component (Wilson and Brauer, 2006).

Gower and McColl (2005) developed a model (PEARLS: Particulate Exposure from Ambient to Regional Lung by Subgroup) that predicts exposure distributions to ambient $\text{PM}_{2.5}$ for 11 age–gender population subgroups in Toronto. The model focused on ambient $\text{PM}_{2.5}$ only, and did not include exposure to indoor-generated $\text{PM}_{2.5}$. For input to the model, the normalized lognormal distribution of ambient $\text{PM}_{2.5}$ was defined with a mean of 15 $\mu\text{g}/\text{m}^3$, reflecting $\text{PM}_{2.5}$ levels previously measured at Toronto stations in the NAPS network. Average “breathing zone” concentrations (i.e. personal exposure) were estimated based on time-activity and microenvironmental level data, assuming only two microenvironments: “indoor” and “outdoor.” Time spent “in-vehicle” was categorized as time spent “outdoors.” Time-activity distributions were estimated from the Toronto subgroup data from the CHAPS study by Leech et al. (1996) for six age groups and males and females separately. Ambient $\text{PM}_{2.5}$ levels in “indoor” environments were estimated for Toronto residences from the equation

$$C_{\text{in}} = F_{\text{inf}} * C_{\text{out}} \quad (2)$$

where $F_{\text{inf}} = P * \alpha / (\alpha + k)$

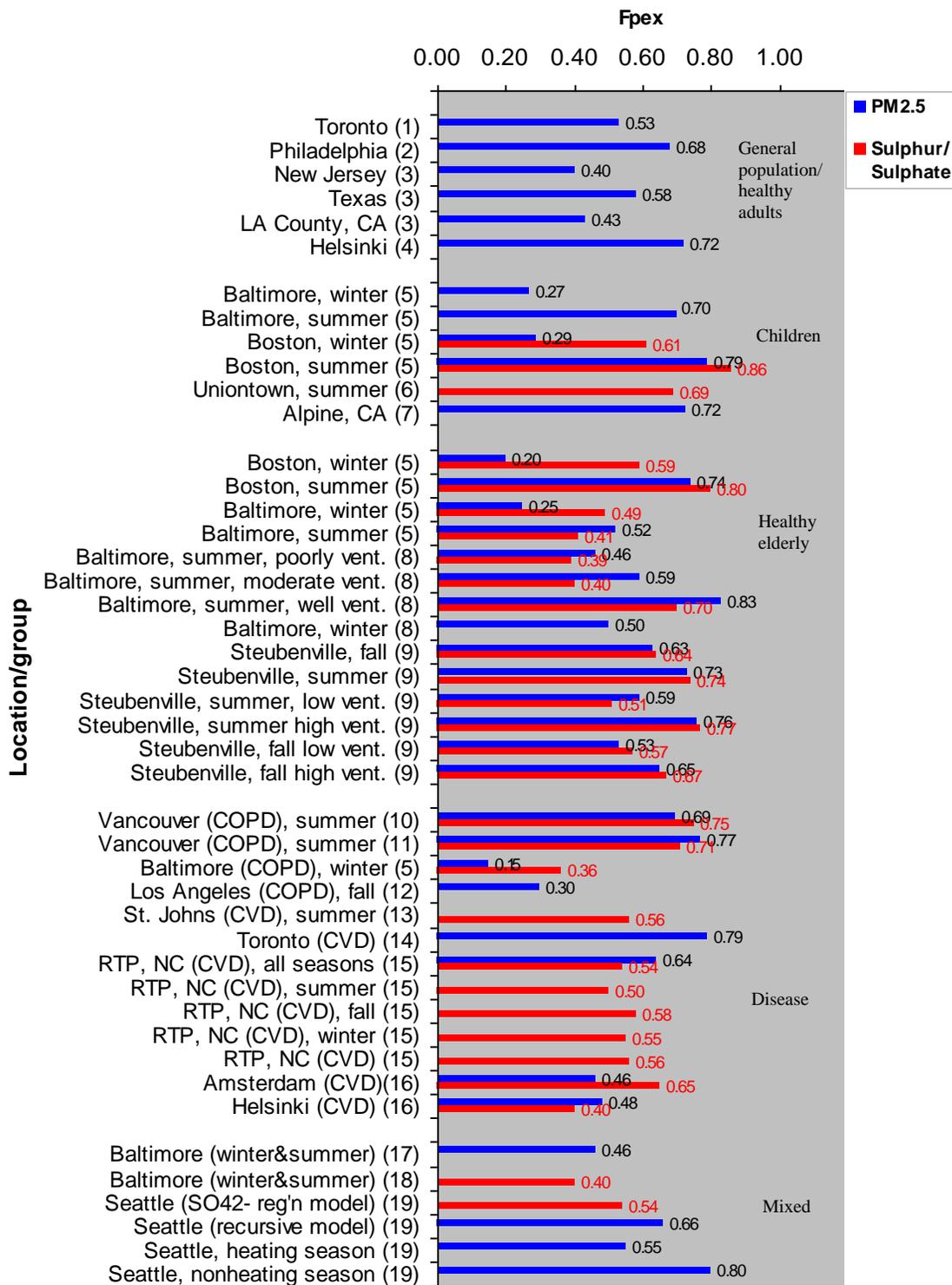
P = penetration

α = AER and

k = particle decay rate.

Penetration was assumed to equal 1, particle decay was assumed to equal 0.39 h^{-1} , both values

Figure 14.7 Mean PM_{2.5} personal exposure factor (F_{pex}) from various studies



References for Figure 14.7:

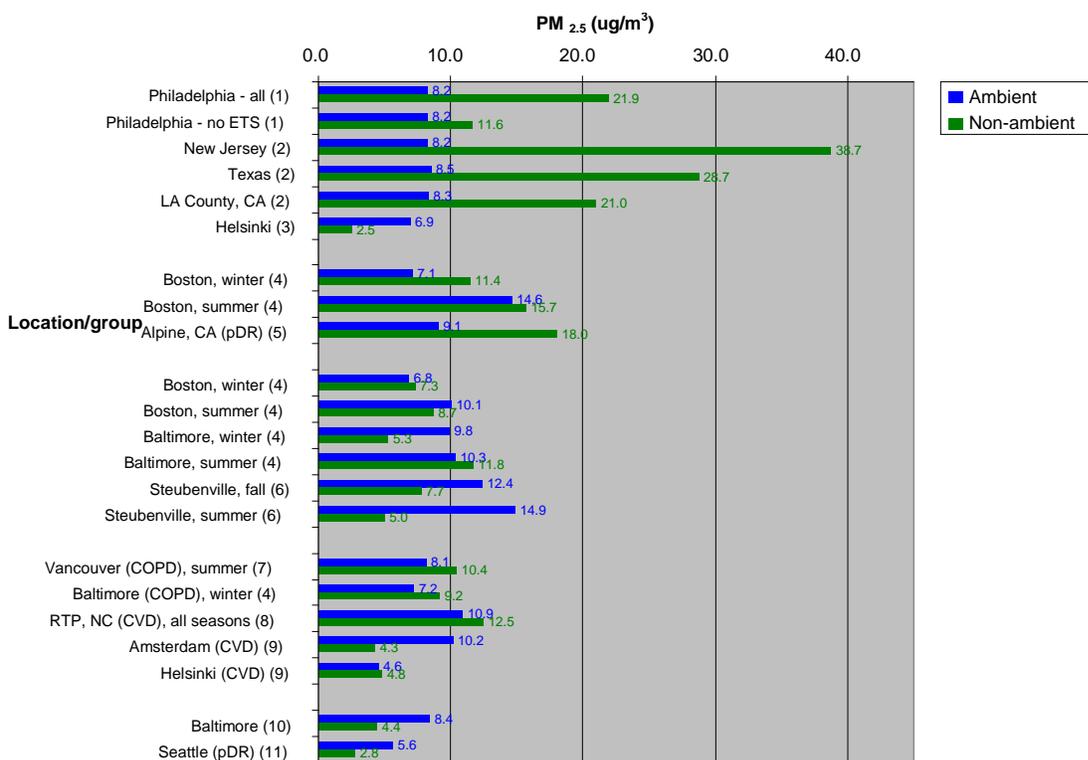
- (1) Gower and McColl (2005)—model, Mean A/mean Co (calc)
- (2) Burke et al. (2001) (medians)—SHEDS model, mean A/mean Co (calc)
- (3) Meng et al. (2005b)—mass balance model, mean A/mean Co (calc)
- (4) Hänninen et al. (2005b)—simulation model, mean A/mean Co (calc)
- (5) Koutrakis et al. (2005)—slope $PM_{2.5}$ P-A and SO_4^{2-} mixed model regression
- (6) Suh et al. (1992)—slope of SO_4^{2-} P-A regression
- (7) Wu et al. (2005b)—recursive P-A model with adjusted pDR data
- (8) Sarnat et al. (2000)—slope of P-A $PM_{2.5}$ and SO_4^{2-} regression
- (9) Sarnat et al. (2006a)—slope of P-A $PM_{2.5}$ and SO_4^{2-} regression
- (10) Ebel et al. (2005)—mean A/mean Co (calc)
- (11) Wilson and Brauer (2006)—slope pooled P-A SO_4^{2-} regression
- (12) Linn et al. (1999)—slope of pooled $PM_{2.5}$ P-A regression
- (13) Stieb et al. (1998)—slope of pooled P-A SO_4^{2-} regression
- (14) Kim et al. (2005)—mean slope of individual P-A $PM_{2.5}$ regressions
- (15) Wallace et al. (2006b)—mean sulphur P/A ratio
- (16) Janssen et al. (2005)—slope of P-A $PM_{2.5}$ and SO_4^{2-} regression
- (17) Williams et al. (2000d)—slope of P-A $PM_{2.5}$ regression
- (18) Landis et al. (2001)—slope of P-A $PM_{2.5}$ and SO_4^{2-} regression
- (19) Allen et al. (2004)—mean sulphur P/O ratio and recursive model

based on the PTEAM Study in Riverside, CA (Özkaynak et al., 1996) and air exchange was modelled as a lognormal distribution with a mean of 0.39 h^{-1} , SD 0.3 h^{-1} , based on air exchange data from Toronto residences measured by Fellin and Otson (1997). Note that exposures to ambient $PM_{2.5}$ in all indoor environments are based on residential estimates, and that the model does not include exposure to indoor-generated PM, just ambient PM. The predicted “breathing zone” distributions were roughly similar across all 11 subgroups. All distributions appear to be normally distributed, with a mean exposure to ambient $PM_{2.5}$ of about $8 \mu\text{g}/\text{m}^3$ (mean $F_{\text{pex}} = 8 \mu\text{g}/\text{m}^3 / 15 \mu\text{g}/\text{m}^3 = 0.53$), and maximum values below $14 \mu\text{g}/\text{m}^3$.

Other mean or median estimates of F_{pex} (Figure 14.7) and ambient/non-ambient components of personal exposure (Figure 14.8) for $PM_{2.5}$ are available from a number of US and European studies. Mean F_{pex} s across studies range from 0.15 to 0.79, due to variations across seasons, communities and possibly population subgroups (based on disease status, age). As shown in Figure 14.8, a few studies reported higher ambient components of personal exposure during the summer, compared with fall or winter: children in Boston, MA, and Baltimore, MD (Koutrakis et al., 2005), seniors in Boston and Baltimore (Koutrakis et al., 2005), and seniors in Steubenville, OH (Sarnat et al., 2006a). These findings were presumably due to higher infiltration rates with more open windows and doors, and perhaps more time spent outdoors.

There is no apparent evidence of large differences in mean F_{pex} between the various population subgroups (Figure 14.7), but the number of studies carried out to date is limited. Allen et al. (2004) did not find differences in mean F_{pex} among four different groups in Seattle, WA (COPD, CHD, healthy elderly, and asthmatic children). Similarly, there are no apparent differences in the mean ambient component of personal exposure across the various study groups (Figure 14.8). There is some evidence that the non-ambient component of personal exposure is higher in studies of the general population compared with other health-compromised subpopulations. This may be expected, if exposures from indoor sources and personal activities are reduced in the health-compromised population, but the dataset is very limited, making it difficult to draw any firm conclusions.

Figure 14.8 Mean ambient and non-ambient source contributions to total PM_{2.5} personal exposure



References for Figure 14.8:

- (1) Burke et al. (2001) (medians)—SHEDS model
- (2) Meng et al. (2005a) (JEAEE)—mass balance model mean A = Mean Et-mean NA (calc)
- (3) Hänninen et al. (2005b)—simulation model
- (4) Koutrakis et al. (2005)—mean A = mean C_{out} * mean F_{pex} (calc)
- (5) Wu et al. (2005b) (adjusted pDR)—recursive model
- (6) Sarnat et al. (2006a)—mean A = mean C_{out} * mean F_{pex} (calc)
- (7) Wilson and Brauer (2006)—daily A = daily F_{pex} * daily Co; daily NA = daily Et-daily A
- (8) Wallace et al. (2006b)—mean sulphur P/O ratio
- (9) Janssen et al. (2005)—slope of sulphur P-O regression
- (10) Landis et al. (2001)—slope of sulphur P-O regression
- (11) Allen et al. (2004) (pDR)—recursive model

As with the two Canadian studies (Kim D et al., 2006; Wilson and Brauer, 2006), US and European studies that have estimated F_{pex} s or the ambient/non-ambient components for each individual have reported considerable between-individual variability in these measures. For instance, Wallace et al. (2006b) reported a range of 0.33–0.77 (mean 0.54) for $\text{PM}_{2.5}$ F_{pex} in 37 non-smokers with hypertension or implanted cardiac defibrillators in Raleigh, NC. The ambient component of $\text{PM}_{2.5}$ personal exposure across individuals ranged from 5.6 to 19.3 $\mu\text{g}/\text{m}^3$ (mean 10.9 $\mu\text{g}/\text{m}^3$) while the non-ambient component ranged from 5.1 to 33.0 $\mu\text{g}/\text{m}^3$ (mean 12.5 $\mu\text{g}/\text{m}^3$). In the same study, the ambient component of personal exposure measured by a pDR (unadjusted values), ranged from 8.5 to 24.8 $\mu\text{g}/\text{m}^3$ (mean 15.8 $\mu\text{g}/\text{m}^3$) (Wallace et al., 2006a). In a study of 28 subjects (healthy elderly, elderly with COPD or CHD, asthmatic children) in Seattle, Allen et al. (2004) used a recursive model with hourly nephelometer measurements to estimate a mean F_{pex} of 0.66 (range 0.25–1.0). In a study of elderly subjects living in a retirement residence in Baltimore, F_{pex} ranged from 0.21 to 0.77 (mean 0.46) (Williams et al., 2000d), based on the slopes of individual $\text{PM}_{2.5}$ P-O regressions; 0.22–0.83 based on P-A regressions. Burke et al. (2001) used a model to estimate the ambient and non-ambient components of $\text{PM}_{2.5}$ personal exposure for the population of Philadelphia and found that variability in the ambient component was similar across all age groups. The authors reported that the variability in the ambient component was less than the variability in total $\text{PM}_{2.5}$ personal exposure (and the non-ambient component), suggesting that human activities do not have a huge impact on ambient exposures.

It is interesting to note that, across studies, the ambient component to indoor $\text{PM}_{2.5}$ is generally higher than the non-ambient component; but for personal exposure, the non-ambient component is generally larger than the ambient. This is most likely a reflection of personal exposure that is occurring in microenvironments that are not captured by indoor monitors, for instance, in traffic, or while cooking or cleaning (the latter is sometimes referred to as the “personal cloud”). This microenvironmental exposure is typically included in the estimate of the non-ambient component of personal exposure, while it is not included in the indoor levels measured by an indoor monitor.

PM₁₀: Ott et al. (2000) carried out a regression analysis using the personal and outdoor (near home) PM_{10} results from the large RTI Toronto, ON, study described earlier (Section 14.1.5.1.1). A general population study, it involved both smokers and non-smokers; each participant provided one 72-h PM_{10} personal exposure sample. The mean ambient PM_{10} concentration was 27.9 $\mu\text{g}/\text{m}^3$ (SD 7.8 $\mu\text{g}/\text{m}^3$) and the mean personal exposure was 69.7 $\mu\text{g}/\text{m}^3$ (SD 85.0 $\mu\text{g}/\text{m}^3$). The slope of the pooled personal–outdoor PM_{10} regression, an estimate of F_{pex} , was 0.61, indicating that on average the participants were exposed to 61% of the ambient PM_{10} . The authors estimated that the average personal exposure to non-ambient PM_{10} was 52.6 $\mu\text{g}/\text{m}^3$ and, by subtraction, the average personal exposure to ambient PM_{10} was 17.2 $\mu\text{g}/\text{m}^3$. They also reported similar analyses using data from two other cities. The mean non-ambient components for Riverside, CA, and Phillipsburg, NJ, were very similar to the Toronto findings: 59.2 and 52.4 $\mu\text{g}/\text{m}^3$, respectively. The mean ambient components of personal exposure were 51.3 $\mu\text{g}/\text{m}^3$ and 33.2 $\mu\text{g}/\text{m}^3$, respectively, reflecting the higher ambient PM_{10} concentrations in these two communities (94.1 $\mu\text{g}/\text{m}^3$ in Riverside and 60.9 $\mu\text{g}/\text{m}^3$ in Phillipsburg, compared with 27.9 $\mu\text{g}/\text{m}^3$ in Toronto). Ott et al. (2000) hypothesized that the mean non-ambient component of PM_{10} exposure may be similar across communities, as seen with these three studies. By contrast, there appears to be more variability in estimates of mean non-ambient exposures among the $\text{PM}_{2.5}$ studies (Figure 14.8).

The mean ambient PM_{10} level measured in the Ebel et al. (2005) study of COPD patients in Vancouver, BC, was 17 $\mu\text{g}/\text{m}^3$ (range 7–36 $\mu\text{g}/\text{m}^3$), while the mean exposure to ambient PM_{10}

was estimated to be $10.3 \mu\text{g}/\text{m}^3$, with considerable variability across individuals (range $1.5\text{--}23.8 \mu\text{g}/\text{m}^3$). This result suggests a mean F_{pex} of 0.61 ($10.3/17$), identical to that reported for the Toronto study.

PM_{10-2.5}: Ebel et al. (2005) did not directly measure personal PM_{10-2.5} in their Vancouver study; however, in Wilson and Brauer (2006), the authors provided an estimate of F_{pex} and the mean ambient contribution to personal exposure for PM_{2.5-10} by using the sulphate measurements and estimated values of $P = 1$ and $k = 0.2$ for sulphate in a mass balance model, to estimate the AERs for each subject on each day. Daily, individual estimates of F_{pex} and the ambient component of personal exposure to coarse PM were then estimated using (a) estimates of daily AERs, (b) fraction of time spent outdoors, and (c) estimated values of $P = 1$ and $k = 1.0$ for PM_{10-2.5} using the mass balance model. The estimated mean ambient contribution to personal exposure was $2.5 \mu\text{g}/\text{m}^3$ (SD $2.1 \mu\text{g}/\text{m}^3$), ranging from -0.4 to $13.5 \mu\text{g}/\text{m}^3$. The mean ambient PM_{10-2.5} concentration was $6.1 \mu\text{g}/\text{m}^3$, suggesting a mean F_{pex} of $2.5/6.1 = 0.41$, considerably lower than the F_{pex} estimate for PM_{2.5} from the same study ($0.71\text{--}0.77$), as described above.

EC: In a study of senior adults in Steubenville, OH, the F_{pex} for EC was estimated from the coefficient of a personal–ambient EC linear fixed-effect model (Sarnat et al., 2006a). The mean F_{pex} was much lower in the summer (0.33) than in the fall (0.70). Also in the summer, the mean F_{pex} was considerably lower than that for sulphate (0.74) or PM_{2.5} (0.73), suggesting a lower effective penetration efficiency for EC. However in the fall, the mean F_{pex} for EC was slightly higher than that for SO_4^{2-} or PM_{2.5} (0.70 vs. 0.64 , 0.63 , respectively). The authors note, however, that the summertime EC measurements had a very high field limit of detection (LOD), hence making the summertime results less reliable. In the fall, the mean EC F_{pex} was slightly higher for people who spent time indoors with open windows than for people who spent no time indoors with open windows (0.73 vs. 0.66). Similar results were found in the summertime data (0.41 vs. 0.13 for “high” vs. “low” ventilation status).

In summary, the three PM_{2.5} Canadian field studies focused on elderly individuals with pre-existing disease. Two studies estimated F_{pex} for each individual in the study, and in both cases, these varied widely, suggesting wide variations between people in time spent outdoors and residential building parameters that affect infiltration. The average F_{pex} estimates in these studies ranged from 0.53 to 0.79 . The means of the ambient PM_{2.5} levels were similar ($11\text{--}15 \mu\text{g}/\text{m}^3$) and the estimates of the mean ambient component of personal exposure were also very similar ($8.0\text{--}8.7 \mu\text{g}/\text{m}^3$). This agrees well with the mean exposure modelled by Gower and McColl (2005) for Toronto, ON, residents of various age and gender groups ($8 \mu\text{g}/\text{m}^3$). The RTI study of the general population in Toronto and a small study of COPD patients in Vancouver, BC, both provided an estimate of the mean F_{pex} of 0.61 for PM₁₀, which is in the range of the F_{pex} s found in the PM_{2.5} studies. For comparison purposes, Ott et al. (2000) also reported on F_{pex} s for PM₁₀ data from Phillipsburg, NJ, and Riverside, CA. The F_{pex} s from these two communities were 0.54 and 0.55 , respectively, slightly lower than Toronto. However, ambient levels were significantly higher in these communities (means of 60.9 and $92.4 \mu\text{g}/\text{m}^3$, respectively), so the ambient components of exposure were much higher (means of 85.6 and $110.5 \mu\text{g}/\text{m}^3$, respectively). Interestingly, the non-ambient components of exposure estimated from the three communities were very similar (means of $52.4\text{--}59.2 \mu\text{g}/\text{m}^3$). One estimate of F_{pex} for coarse PM from a study of COPD patients in Vancouver found a lower F_{pex} compared with PM_{2.5}, consistent with lower F_{in} s reported for coarse PM.

14.1.7.2.3 Determinants of F_{inf} and F_{pex} and ambient components of total personal exposure

Particle size: PM infiltration is strongly dependent on particle size (Abt et al., 2000b; Long et al., 2001a; Morawska et al., 2001; Zhu et al., 2005), due to particle size effects on the deposition rate, k , and the penetration factor, P .

In regard to k , the theory of particle deposition predicts a U-shaped curve with respect to particle diameter (Nazaroff, 2004). The high deposition velocities of the UFPs are due to their higher Brownian motion, causing them to collide and stick with all surfaces (ceilings and walls as well as floors). The high deposition velocities of coarse PM are due to the importance of gravitation in causing these particles to settle out on horizontal surfaces.

A number of experimental studies have measured k 's (Thatcher et al., 2002; Lai, 2002; Riley et al., 2002; Thatcher et al., 2003; Chao et al., 2003; Liao C-M et al., 2004; Wallace et al., 2004a, 2004b; He et al., 2005; Hussein et al., 2005). These studies usually show the U-shaped curve, but often the measured rates are higher, sometimes an order of magnitude higher, than the predicted theoretical rates. In the PTEAM study in Riverside, CA, based on the combined day and night 12-h data, PM_{10} had a higher mean k than fine particles ($0.65 \pm 0.28/h$ vs. $0.39 \pm 0.16/h$) (Özkaynak et al., 1996b).

Vette et al. (2001) estimated k 's for particles of from 0.01 to 2.5 μm in a detached residence (with no indoor sources) in a retirement community in Fresno, CA, during two 4-week periods during winter and spring 1999. Within the submicron range, k 's were highest for the smallest UFPs (around 2.5/h), decreasing with increasing particle size to about 0.4/h for 0.1 μm particles. Rates were lowest for particles between 0.1–0.5 μm and then increased again with increasing particle size to about 4/h for particles around 2 μm in diameter. The authors noted that measured rates were consistent with model predictions up to about 0.4 μm ; for larger particles the experimentally determined k 's were considerably higher than model results, suggesting the possibility of an additional indoor loss mechanism.

Chao et al. (2003) estimated k for five particle size groups (from 0.02 to 10 μm) in six non-smoking residences in Hong Kong from October 2001 to March 2002. A U-shaped deposition curve was found with the minimum mean k of 0.27/h (SD = 0.25) for the 0.542–0.777 μm size bin. The k 's increased for decreasing particle sizes lower than 0.542 μm ; the ultrafine size bin had a mean k of 0.52/h (SD = 0.32). Similarly, k 's increased with increasing sizes higher than 0.777 μm ; the largest particles (4.698–9.647 μm) had the maximum mean k of 1.00/h (SD = 0.56).

Zhu et al. (2005) estimated k (and P) for particles of diameter 6–200 nm, collected in four apartments that were all within 15–40 m of the sound barrier beside the I-405 Freeway in Los Angeles, CA. Indoor and outdoor particle size distributions were measured during a minimum of six 24-h periods from October to December 2003 in one bedroom in each apartment, with the door closed to minimize contamination from indoor activities. A dynamic mass balance model that accounted for changes in outdoor PN was fitted to the PN data collected while the window was closed and the fan was off, in order to estimate the deposition and penetration rates across the size fractions. The curve describing the mean k as a function of particle size had a U-shape for particles between 20 nm and 200 nm with a mean k of 0.9 for 20 nm and 200 nm particle diameters, and a minimum of 0.6 for particles of 100 nm. Below 20 nm, the curve decreased to about 0.6 for the smallest particle sizes (6 nm), contrary to the theoretical curve.

K 's were measured in an occupied townhouse in Reston, VA, between July 1999 and June 2001 for 128 size categories ranging from 0.01 to 5.4 μm using a SPMS/APS monitor (Wallace et al., 2004a) and for larger particles (0.3–20 μm) using a CLIMET monitor (Howard-Reed et al.,

2003) to examine the effects of a furnace fan, furnace filter and electrostatic precipitator. With increasing particle size, k 's increased and F_{inf} decreased for all ventilation and filtration settings. Wallace et al. (2004a) found that k 's followed a U-shaped distribution, with the minimum rate occurring near 0.1 μm . K 's ranged from 0.7 to 5.32/h when the furnace fan was off. Howard-Reed et al. (2003) reported that the mean k increased from 0.30 for particles 0.3–0.5 μm in size to 1.4 for particles 2.5–5 μm . Based on this dataset, the F_{inf} estimated for low AER conditions ($\alpha = 0.2/\text{h}$) (and central fan off) decreased from 0.40 for particles 0.3–0.5 μm in size to 0.13 for particles 2.5–5 μm . Under higher AER conditions (mean AER = 1/h), the F_{inf} decreased from 0.77 to 0.42 across the same size categories.

Similarly, P s are theoretically lower for smaller and larger particles (Nazaroff, 2004), since coarse particles passing through a crack in the building envelope may settle out before traversing the entire length of the crack, and UFPs may hit the sides or top or bottom of the crack before making it through.

Because of the difficulty of measuring penetration, there are few experimental studies. The large-scale PTEAM study used non-linear estimation techniques to calculate a P of unity for both PM_{10} and $\text{PM}_{2.5}$ particles. In the study by Vette et al. (2001) described above, the P 's for all particle sizes ranged between 0.5 and 0.9, with slightly lower P for particles around 0.04 μm ; however, the penetration factors observed for particles >0.04 μm were considerably larger than expected. In the study by Chao et al. (2003) described above, the P had a hill shape, with the medium-sized particles (between 0.835 and 1.382 μm) having the maximum mean penetration coefficient of 0.79. Lower penetration coefficients were obtained in both larger and smaller particle size bins. The particles between 0.02 and 1.00 μm in size had a mean penetration coefficient of 0.64. The largest particles, in the 4.698–9.647 μm size bin, had the minimum penetration coefficient of 0.48. In the study by Zhu et al. (2005) looking at UFPs, the mean penetration factor was relatively constant (around 0.5) for particles of between 20 nm and 200 nm, with decreasing P for particles of less than 20 nm (to about 0.15).

With respect to F_{inf} , several studies have shown that particles in the accumulation mode size (0.1–1.0 μm) have the largest F_{inf} (higher penetration efficiencies and lower deposition rates), while ultrafine (0.0–0.1 μm) and coarse (1.0–10.0 μm) particles have the lowest F_{inf} due to lower penetration coefficients and higher deposition velocities (Raunemaa et al., 1989; Kulmala et al., 1999; Tung and Chao, 1999; Abt et al., 2000b; Long et al., 2001a; Vette et al., 2001; Levy et al., 2002; Sarnat et al., 2002; Hänninen et al., 2004; Zhu et al., 2005). For example, Long et al. (2001a) estimated the infiltration factor for $\text{PM}_{2.5}$ and various particle sizes in nine non-smoking homes in the Boston area, during spring/summer and fall/winter 1998. The infiltration factors were estimated by calculating the indoor/outdoor ratios of continuous indoor and outdoor $\text{PM}_{2.5}$ and size distribution measurements made in each study home over a weeklong period by matching nightly average indoor/outdoor data. The authors reported a mean $\text{PM}_{10-2.5}$ F_{inf} of 0.28 compared with a mean $\text{PM}_{2.5}$ F_{inf} of 0.74 from the same homes. Looking across a range of size categories, they found that F_{inf} increased with increasing particle size through the 0.02–0.3 μm size fraction and then decreased with increasing particle size through the 0.3–10 μm size fraction. The infiltration factors had a GM value of 0.52 for ultrafine PM (0.02–0.03 μm size intervals) and 0.16 for coarse PM (6–10 μm size intervals). The largest GM infiltration factors, ranging from 0.70 to 0.73, were found for particles in the accumulation mode (0.08–0.5 μm size intervals). The authors note that the peak in the accumulation mode coincides with a minimum in deposition velocity where neither loss mechanism is significant. They also noted that fine particles demonstrated greater variability in the infiltration factor than coarse particles.

Geller et al. (2002) also reported a much larger mean F_{inf} for $\text{PM}_{2.5}$ (0.74) than for $\text{PM}_{10-2.5}$ (0.3) in a study of 13 homes in Coachella Valley (desert), CA.

Franck et al. (2003) measured the indoor–outdoor ratio of PN among particles of between 15 and 800 nm in a laboratory without significant indoor sources. The I/O ratio was highest (median around 0.4) for particles in the 100–200 nm range, and lowest for the smallest particles (median I/O < 0.1 for particles <35 nm). The median I/O also decreased for larger particles (median I/O 0.2 for particles around 500–600 nm).

In the study by Zhu et al. (2005) described above, AERs and PNs were measured under three different ventilation conditions: closed window with fan off (80% of measurements), closed window with fan on (10% of measurements) and open window with fan off (10% of measurements). The data were averaged over the three ventilation conditions to estimate I/O ratios. In all four apartments, day and night I/O ratios increased across size fractions from 20 nm to 100 nm; daytime I/O ratios were higher (0.5–1.0) than nighttime (0.2–0.6). Below 20 nm, the downward trend in I/O ratios did not continue as expected: instead, the I/O ratios increased. The authors suggest that this may be due to low instrument detection limits, secondary organic aerosol formation, or the loss of volatile components by particles in the 20–40 nm size range, producing particles of 20 nm or less, as has been reported by other authors (Lunden et al., 2003b; Kuhn et al., 2005). Much lower I/O ratios were observed when the heating, ventilating and air conditioning (HVAC) system fan was on, possibly due to partial filtering of the air by the ventilation system, thus reducing indoor concentrations. During open-window periods, the I/O ratio was very close to 1.0 across all particle sizes.

Hussein et al. (2005) measured F_{inf} in an unoccupied naturally ventilated non-smoking home in Espoo, Finland, in February 2001. F_{inf} was estimated using I/O ratios during a period of 5 d with no indoor sources. F_{inf} had a median of 0.36 for UFPs (diameter <100 nm) and 0.60 for particles >100 nm in diameter. The F_{inf} (0.66) was highest for particles of between 100 and 400 nm in diameter.

In the PTEAM study carried out in Riverside, CA, Özkaynak et al. (1996b) found that the PM_{10} infiltration factor was lower than F_{inf} for $PM_{2.5}$ (0.6 vs. 0.7, respectively).

Few data are available comparing F_{pex} for coarse and fine particles. As discussed previously, Wilson and Brauer (2006) estimated the ambient component of personal exposure for both $PM_{2.5}$ and $PM_{10-2.5}$ for a group of 16 COPD patients in Vancouver, BC, from April to September 1998. Using the mean estimates of ambient exposure and the mean ambient PM levels, the estimated mean F_{pex} for $PM_{2.5}$ was 0.71, considerably higher than that calculated for $PM_{10-2.5}$ (0.41).

Ventilation/AER (α): The AER, α , is an important parameter affecting PM infiltration. Penetration efficiency, P , approaches unity when AERs are high and the majority of ambient particles have less interaction with the building shell. When AERs are low, penetration efficiency is influenced by the particle deposition rate (US EPA, 2004, Vol. I, p. 5–77).

A number of studies have examined the relationships between F_{inf} and AERs (Wallace, 1996; Wilson and Suh, 1997; Wilson et al., 2000; Abt et al., 2000a; Long et al., 2000, 2001a, 2001b; Liu and Nazaroff, 2001; Mosley et al., 2001; Thornburg et al., 2001; Sarnat et al., 2002; Allen et al., 2003; Williams et al., 2003b, Fig. 4; Hänninen et al., 2004, 2005b; Kopperud et al., 2004; Long and Sarnat, 2004; Hussein et al., 2005; Meng et al., 2005b; Zhu et al., 2005). Many of these studies have found that F_{inf} has a strong relationship with AERs for particles of all sizes.

Looking at the equation for F_{inf}

$$F_{inf} = Pa/(\alpha + k) \quad (3)$$

when α is small ($<k$), F_{inf} will be less than half, even if P is at its maximum of 1. When α is large ($>k$), F_{inf} approaches the value of P , which itself approaches the value of 1, because open

windows allow the particles in with no resistance. So the graph must start low and approach an asymptote of 1. On the other hand, there is no simple graphical relationship between F_{inf} and α , because different homes have different values of P and k . In one of the larger studies of 37 homes in Research Triangle Park, NC ($n = 720$ person-days), sulphur measurements were used to determine F_{inf} . F_{inf} increased rapidly as α progressed from 0 to approximately 0.5/h; at higher α , F_{inf} increased more gradually to a plateau slightly greater than 0.8 when the AER was greater than about 1.5/h. Long and Sarnat (2004) measured the nighttime indoor–outdoor ratios as estimates of F_{inf} for various elements, in nine Boston, MA, homes. They found that the infiltration factors for sulphur, Ni, Zn, Fe, K and Si appeared to plateau at values between 0.8 and 1.0 as AERs increased to values exceeding 1 or 2/h. AER is determined by various factors such as building parameters, meteorological conditions, mechanical ventilation, window use and A/C. In turn, some of these factors are determined by geographic location and season.

Geographic location and season: A colder climate, as found in Canada, favours more tightly sealed buildings and closed windows, resulting in lower AERs. A number of studies have looked at the seasonal variability of AERs and F_{inf} (Brauer et al., 1991; Leaderer et al., 1999; Long et al., 2000, 2001a, 2001b; Sarnat et al., 2002; Kinney et al., 2002; Liu L-JS et al., 2003; Allen et al., 2003; Sørensen et al., 2005a; Wallace and Williams, 2005). Generally these studies found that AERs and F_{inf} were typically higher in summer than in winter.

In the Boston, MA, study by Long et al. (2001a), described previously in sections 14.1.7.2.1 and 14.1.7.2.3, 100% of summertime hourly F_{inf} s for $PM_{2.5}$ were greater than 0.7, while 73% of the hourly fall/winter F_{inf} s were less than 0.7. The mean AER was 4.9/h (SD = 3) in summertime and the mean was 0.62/h (SD = 0.24) in wintertime. Also, the mean estimate of P was higher in the summer (1.11) than in the winter (0.54). The mean estimates of k for $PM_{2.5}$ were similar between both seasons (0.15/h (summer) vs. 0.10/h (winter)). Similarly, in a study of six non-smoking homes in Boston, Sarnat et al. (2002) reported a mean F_{inf} during the fall/winter of 0.47 compared with a mean F_{inf} in the spring/summer of 0.72.

In a study of 44 residences conducted in Seattle, WA, Allen et al. (2003) found the mean F_{inf} was higher in the non-heating season (0.79/h (SD = 0.18)) than during the heating season (0.53/h (SD = 0.16/h)). This was true for both private homes (0.76/h vs. 0.49/h) and apartments (0.82/h vs. 0.56/h). The non-heating season had higher mean AER (0.72/h (SD = 0.82/h) (non-heating) vs. 0.37/h (SD = 0.17) heating), higher P (0.99/h (SD = 0.03) (non-heating) vs. 0.89/h (SD = 0.11) (heating)), while k was lower in the non-heating season than in the heating season (0.12/h (SD = 0.08) vs. 0.27/h (SD = 0.18), respectively). Similarly, the mean F_{pex} was higher in the non-heating season (0.80 (SD = 0.17)) than in the heating season (0.55 (SD = 0.16)) (Allen et al., 2004).

Wallace et al. (2006b) found less variation in mean F_{inf} s across seasons (summer 0.5, fall 0.63, winter 0.63 and spring 0.62) in a study of 29 African-Americans with hypertension and 8 with implanted cardiac defibrillators, despite a fairly wide range of mean AERs across the seasons (summer 0.49/h, fall 0.61/h, winter 1.01/h and spring 0.68/h).

Koutrakis et al. (2005) found mean $PM_{2.5}$ F_{pex} s to be higher in summer than in winter among Boston, MA, children (0.72 vs. 0.29), Baltimore, MD, children (0.70 vs. 0.27), Boston seniors (0.72 vs. 0.20) and Baltimore seniors (0.52 vs. 0.25) based on the slope of a $PM_{2.5}$ mixed regression model (see Figure 14.7 also). Sarnat et al. (2006a) also reported slightly higher mean F_{pex} s during the summer compared with the fall in a cohort of seniors living in Steubenville, OH (0.74 vs. 0.64, based on the slope of the personal–ambient SO_4^{2-} regression model).

Hänninen et al. (2005b) found that $PM_{2.5}$ infiltration factors for 98 homes in Helsinki, Finland, were higher during summer; they attributed this to seasonal adjustments in building ventilation.

An exception to the general trend of higher AERs during warmer, summer months is in air-conditioned homes, where AERs are generally lower during the summer when the A/C is in use. For example, in a study of 37 participants with hypertension or implanted defibrillators from Raleigh, NC, AERs and F_{inf} were lowest in the summer, attributed to the high prevalence of use of A/C. The ambient contribution to personal exposure was highest in the winter when AERs were the highest (mean 1.01/h) (see Table 14.2) (Wallace et al., 2006b). In a study of six Boston homes, Sarnat et al. (2002) found that the average AER measured in one newer, air-conditioned home was 0.18/h in spring/summer compared with 0.31/h in fall/winter. Long et al. (2001a) also reported very low AERs (mean 0.16/h, SD = 0.02/h) in a Boston study home, attributed to the heavy use of a central HVAC system during a warm and humid July sampling period; the house was kept tight, so indoor air was cooled and recirculated within the house.

Table 14.2 Mean air exchange rate (AER), F_{inf} and outdoor contribution to personal exposure, by season (Raleigh, NC, panel study) (Source: Wallace et al., 2006b)

Season	AER (/h)	F_{inf} (S_{in}/S_{out})	Ambient contribution to personal exposure ($\mu\text{g}/\text{m}^3$)
Summer	0.49	0.50	11.3
Fall	0.61	0.63	12.4
Winter	1.01	0.63	13.5
Spring	0.68	0.62	9.4

Meteorological conditions (temperature, wind speed and direction, solar irradiation):

AERs increase with increasing indoor–outdoor temperature differences (Long et al., 2000; Wallace et al., 2002; US EPA, 2004). Also, the AER may increase with solar irradiation by increasing outdoor temperature (Chan, 2002).

Wallace et al. (2002) studied the effects that temperature and wind had on AERs over all four seasons of the year at an occupied non-smoking three-story townhouse in Virginia, from January 2000 to January 2001. A multiple regression of AER on indoor–outdoor temperature difference, wind speed and wind direction was performed on data collected during periods with a minimum of window opening (overnight, during the six coldest months—October through March). It appears that the indoor–outdoor temperature differences clearly affected the AER: it increased by 0.0156/h/°C (SE = 0.0005/h). The indoor–outdoor maximum temperature difference of 34 °C corresponded to an effect on AER equal to 0.5/h. Wind speed had no effect on the AER, while wind direction had a tiny effect, increasing the rate by 0.016/h (SE = 0.003/h) only when the wind was from the east.

Natural ventilation (window use): Wallace et al. (2002) studied the effects of window-opening behaviour and use of fans on AERs, at an occupied non-smoking three-story townhouse in Virginia, over a 1-year period starting in January 2000. Although higher AERs of 3–4/h were measured for short time periods, the mean maximum rate over 12–36 h was 2/h, a result of opening multiple windows. The average AER when windows were closed was 0.44/h (SD = 0.15/h), while when the windows were open or the attic fan on, the average rate was 1.57/h (SD = 0.73/h). Window opening showed a strong seasonal effect: the windows were kept open and/or the attic fan was in use more than 50% of the time during the summer months, while during the fall and winter months the windows were kept closed more than 90% of the time. An attic fan was used 20% of the time during the summer and 11% of the time during the rest of the

year. The AER increased from a mean of 0.55/h when the attic fan was off to a mean of 1.55/h when the fan was on. The use of a furnace fan seemed to have no effect on the AER.

In a study of 44 Seattle, WA, homes, Allen et al. (2003) reported a mean F_{inf} of 0.69 on open-window days and 0.58 on closed-window days. The mean AER was considerably higher in the non-heating season (0.72/h) than in the heating season (0.37/h) and the corresponding mean \pm SD percentage of days with at least one open window was also significantly higher ($p < 0.01$) during the non-heating season ($70.4 \pm 37.5\%$) than in the heating season ($42.1 \pm 38.5\%$).

Sarnat et al. (2000) looked at F_{pex} during the summer for 20 older adults living in single-family houses or apartments (all except one home had A/C) in Baltimore, MD. The ventilation status of the home was used to separate the homes into three categories: well ventilated had open windows more than 72% of the time, moderately ventilated had windows open 4–72% of the time and poorly ventilated had open windows less than 4% of the time. The F_{pex} , estimated by the slope of a personal–ambient $PM_{2.5}$ mixed-effects model, was 83% for the well-ventilated homes, 59% for the moderately ventilated homes and 46% for the poorly ventilated homes. The slopes of a personal–ambient model for SO_4^{2-} also decreased with ventilation status (0.70 (well ventilated), 0.40 (moderately ventilated) and 0.39 (poorly ventilated)).

Sarnat et al. (2006a), in a study of senior adults in Steubenville, OH, reported a mean F_{pex} (based on the slope of a personal–ambient SO_4^{2-} regression) of 0.77 for individuals spending time in indoor environments with open windows during the summer, significantly higher than for individuals spending no time indoors with open windows (mean slope 0.51). Similar results were found in the fall (mean F_{pex} 0.67 (open windows) vs. 0.57 (closed windows)).

Air conditioning and mechanical ventilation/circulation: Wallace et al. (2004a) measured deposition rates for particles in 128 size categories from 0.01 to 5.4 μm in an occupied townhouse in Reston, VA. The use of a central fan did not increase the AER (Wallace et al., 2004b); however, except for the smallest UFPs ($<0.02 \mu m$), particle deposition rates were higher when the fan was on, even when no filter was installed or working. Deposition rates with the furnace fan off showed the theoretical V shape discussed in Section 14.1.7.2.3.1, with the minimum occurring at particle diameters of about 0.1 μm . For most particle sizes, deposition rates increased only slightly when the fan was on without a filter, or with just a low-quality furnace filter. A medium-quality in-duct fibrous mechanical filter produced substantial increases in deposition rates for ultrafine and fine particles (up to 2/h), but not for particles in the 0.1–0.5 μm range. Only an in-duct electrostatic precipitator was able to produce very large increases in deposition rate (by 2–3/h) for all particle sizes. In the same study, Howard-Reed et al. (2003) also reported that the use of a central fan increased the deposition rate by between 0.5/h and 2/h for particles 0.3–10 μm . Under high AERs (1.0/h), estimates of F_{inf} were higher when the HVAC was off (from 0.77 for 0.3 μm particles to 0.16 for 10 μm particles) than when the HVAC was on (from 0.56 for 0.3 μm particles to 0.12 for 10 μm particles). Estimates of F_{inf} were lower under lower air exchange conditions (0.2/h), but a similar pattern was found with lower F_{inf} s when the HVAC was off (ranging from 0.4 to 0.04 across the 0.3–10 μm size range) than when it was on (F_{inf} s of 0.21 to 0.03 across the 0.3–10 μm size range).

Use of A/C systems while windows and exterior doors are generally kept closed generally decreases the F_{inf} by decreasing the α , which increases particle residence times and particle removal/deposition rates (Colome et al., 1992; Lai et al., 1999; Leaderer et al., 1999; Abt et al., 2000b; Long et al., 2000, 2001a; Sarnat et al., 2000, 2002; Wallace et al., 2002, 2006b; Allen et al., 2003; Howard-Reed et al., 2003; Thornburg et al., 2004; Hänninen et al., 2005b; Meng et al., 2005b; Wallace and Williams, 2005).

Dockery and Spengler (1981) measured the infiltration factors for fine particles in 68 homes in six US cities (Portage, ME, Topeka, KS, Kingston, NY, Watertown, NY, St. Louis, MO, and

Steubenville, OH) for at least 1 year. It was found that the long-term mean F_{inf} of outdoor fine particulates was about 70% and that use of a central A/C system could reduce this factor by about half. Suh et al. (1992) measured the mean sulphate I/O in the homes of healthy children in Uniontown, PA, in the summer of 1990. They reported a mean I/O ratio (F_{inf}) of 0.69 for air-conditioned homes and 0.86 for non-air-conditioned homes.

In a study of nine non-smoking homes in Boston, MA, previously described in sections 14.1.7.2.1 and 14.1.7.2.3, Long et al. (2001a) found that in one home with a central HVAC system the mean AER was significantly lower in the summertime while the A/C system was in use (mean = 0.16/h) than in the wintertime (mean = 0.31/h).

In the RIOPA study carried out in Elizabeth, NJ, Los Angeles County and Houston, TX (Meng et al., 2005a), the mean ambient contributions to both indoor and personal concentrations were similar in Los Angeles County and Elizabeth, but much lower in Houston. This was attributed to higher rates of A/C use (and resulting reductions in AERs) in Houston (23% A/C use during sampling, compared with <3% in Los Angeles County and 18% in Elizabeth).

Hänninen et al. (2005b) found that the mean $PM_{2.5} F_{inf}$ was higher in residential homes than in workplaces, which presumably have higher use of recirculated and filtered air.

Building age/construction type: Infiltration factors have been found to vary by home age. New homes tend to be tightly sealed and have central A/C systems, both circumstances that result in lower AERs and thus lower infiltration factors (Long et al., 2000, 2001a; Janssen et al., 2002; Sarnat et al., 2002; Allen et al., 2003; Meng et al., 2005b).

In the Boston-area homes study, Long et al. (2001a) demonstrated that, with the exception of coarse PM, the mean F_{inf} s for both seasons were high in an older New England home that had fairly high nighttime AERs in the fall (mean = 0.82/h) and extremely high AERs in the summer (mean = 4.2/h). By contrast, the F_{inf} was substantially lower in both seasons in a newer home with a central HVAC system, which had substantially lower nighttime AERs during both seasons (means of 0.31/h and 0.16/h for wintertime and summertime data, respectively).

Hänninen et al. (2005b) found the mean \pm SD $PM_{2.5} F_{inf}$ was higher in residential homes built before 1990 than in homes built between 1990 and 1997 (0.65 ± 0.19 vs. 0.58 ± 0.21). The authors also report higher mean \pm SD $PM_{2.5} F_{inf}$ for workplaces built before 1990 compared with those built between 1990 and 1997 (0.48 ± 0.25 vs. 0.35 ± 0.12).

Lachenmyer and Hidy (2000) found that infiltration factors ranged from 0.33 (new house) to 0.90 (older house) in 10 air-conditioned homes in Birmingham, AL, and F_{inf} was significantly correlated with building age ($r = 0.60$).

Other building parameters affecting P , k and F_{inf} including mechanical filtration: Particle infiltration depends partly on particle deposition, which is a highly variable process that is also dependent on other site-specific building conditions such as air turbulence and mixing, near surface flows, temperature, surface materials and room volume, nature and composition of particles (electrophoresis and thermophoresis effects) (Nazaroff et al., 1993; Abt et al., 2000b; Long et al., 2001a; US EPA, 2004). For example, PM deposition rates may be higher in a home with large surface areas (many rugs, carpets or fibrous wall hangings) (Wallace et al., 2006b), but this effect is expected to be less pronounced for larger particles for which the deposition is more dominated by gravitational settling (Howard-Reed et al., 2003). Particle surface properties such as their electrostatic characteristics have a significant influence on deposition rate (US EPA, 2004).

PM filtration devices can be effective at reducing particle levels in homes or office buildings (Bowser, 1999; Fisk et al., 2002; Wallace and Howard-Reed, 2002; Howard-Reed et al., 2003;

Wallace et al., 2004a; Hänninen et al., 2004). These devices include portable air cleaners, which are used to reduce particle levels in a room or small area, while whole-house or in-duct air cleaners are installed in the ductwork of a home or office building with central forced air and are designed to reduce particle levels throughout the house. Mechanical filters, such as ordinary furnace filters, intercept particles in the air as they pass through the fibrous material. HEPA (high-efficiency particulate air) filters are extremely densely packed fibreglass filters that, to obtain the HEPA designation, must filter out 99.97% of particles down to 0.3 μm in diameter. HEPA-type filters meet a less stringent standard of 95% efficiency for 0.3 μm particles. This particle size is normally the hardest to filter, so the efficiency should be even greater than 99.97% for other size fractions. Another type of air cleaner uses an electric charge to enhance the collection of particles. This includes electret filters, in which are permanently charged fibres that attract charged or uncharged particles. Electrostatic precipitators (ESPs) add an electric charge to incoming particles and collect the charged particles on collecting plates. Ionizers emit ions (charged particles) into a room, which attach to the PM; the charged particles are then attracted to surfaces within the ion generator itself or surfaces in the home such as floor, walls and furniture.

Generally the ESPs and HEPA filters are the most effective systems (Bowser, 1999; Fisk et al., 2002; Howard-Reed et al., 2003; Rousseau et al., 2003; Wallace et al., 2004a; Chen, 2006). Theoretical calculations suggest that a whole-house effectiveness of about 65% could be expected for a well-performing and well-maintained whole-house ESP (Riley et al., 2002). Fisk et al. (2002) used a mass balance model to estimate the reductions in indoor concentrations of outdoor PM (integrated across 0.01–10 μm size fractions) from the use of air filtration systems, including filters in HVAC systems and stand-alone filters. The authors found that the predicted benefits of low-efficiency filters (ASHRAE 45% and lower) were quite small; however, the predicted reduction was 80% for the ASHRAE 85% rated filter, and 95% for the HEPA filter. Wallace et al. (2004a) compared the effectiveness of an ESP filter, a mechanical filter and no filter (fan on and off) in an occupied townhouse, for reduction of particles in the 0.1–1 μm range. When the system was new the ESP was extremely efficient for all particle sizes: >98% for 2.5–10 μm and 95–98% for the smallest sizes (0.3–2.5 μm). However, after a month or two without cleaning, the efficiencies were reduced to about 20–50%. Overall, the ESP outperformed the other filters by a ratio of about 3:1, corresponding to a 67% reduction in particle levels. Filters are generally best at collecting the smallest (ultrafine) and largest (coarse) particles, with minimum efficiencies for particles in the middle range of 0.2–0.4 μm (Hanley et al., 1994; Bowser, 1999; Agranovski et al., 1999, 2001, 2006; Partti-Pellinen et al., 2000; Fisk et al., 2000, 2002; Thornburg et al., 2001; Emmerich and Nabinger, 2001; Paschold et al., 2003; Wallace et al., 2004a; Nazaroff, 2004; Abadie et al., 2004; Batterman et al., 2005; Hanley and Elion, 2005). For example, Thornburg et al. (2001) estimated the I/O concentration ratios for particles of 0.05, 0.1, 0.2, 0.5, 1.0 and 2.5 μm for three building types (commercial, house with HVAC system and house without HVAC) during periods with no indoor sources using a mass balance indoor air quality model. They found that the I/O concentration ratios for each scenario were greatest for 0.5 μm size particles. Additionally, it was found that an HVAC system in commercial and residential buildings decreased the I/O concentration ratios, particularly for smaller (0.05 μm) and larger (1.0, 2.5 μm) particles. Specifically, for the commercial scenario, the I/O ratios were 0.14, 0.30, 0.32, 0.38, 0.2 and 0.03 for particle sizes 0.05 μm , 0.1 μm , 0.2 μm , 0.5 μm , 1.0 μm and 2.5 μm , respectively. For the house with HVAC, the I/O ratios were 0.20, 0.40, 0.48, 0.55, 0.22 and 0.07 while the house without HVAC had I/O ratios of 0.40, 0.45, 0.50, 0.58, 0.50 and 0.42 for the same particle sizes, respectively.

Riley et al. (2002) estimated the importance of size-dependent removal mechanisms by estimating the F_{inf} during a no-source period for five representative building scenarios: "(i) an office building with a 40% ASHRAE filter (Ofc40); (ii) an office building with an 85% ASHRAE

filter (Ofc85); (iii) a closed residence with continuous central air and a standard furnace filter (ResCA); (iv) a residence with a typical infiltration ventilation rate and no central air (ResTV); and (v) a residence with a high natural ventilation rate as may occur with open windows (ResHV).” The filter efficiency had a large impact on the F_{inf} for $PM_{2.5}$ and PM_{10} . It was found that the 85% ASHRAE filter substantially reduced the F_{inf} for all sizes (except the coarse mode mass) by a factor of approximately 3–4 compared with the 40% ASHRAE filter. Both filters were highly efficient (>99%) at removing small UFPs (<0.01 μm), as well as in the coarse mode (>3 μm). Under high ventilation conditions in a naturally ventilated residence the F_{inf} s for sulphate in $PM_{2.5}$ and EC in $PM_{2.5}$ were both above 0.9, whereas in the residence with a continuously operating central air handler the F_{inf} s for these constituents were both reduced to less than 0.5 (Riley et al., 2002).

In a study of an office building near downtown Helsinki, Finland, Koponen et al. (2001) found that an EU7 type filter removed about 90% of UFPs and 70% of AMPs. In comparison, Hussein et al. (2004) reported that 30% of UFPs and 10% of AMPs were removed by a less efficient EU3 type filter in a downtown Helsinki office.

Howard-Reed et al. (2003) estimated the effect of using an in-duct electronic air cleaner on F_{inf} for 0.3–5 μm particles based on measurements from a non-smoking townhouse with central forced-air fan (HVAC) for two different AERs (high, 1/h; low, 0.2/h). Under the low air exchange assumption, with no air cleaner and the fan off, the estimated F_{inf} ranged from 0.13 for the larger particles (2.5–5 μm) to 0.40 for the smaller particles (0.3–0.5 μm). With the air cleaner on, the estimated F_{inf} s were dramatically reduced, ranging from 0.04 (for the 2.5–5 μm size fraction) to 0.06 (for the 0.3–0.5 μm size fraction). Under the high air exchange assumption, F_{inf} s were considerably higher (0.42–0.77 with no air cleaner and the fan off), but the air cleaner had the same effect of reducing F_{inf} s (0.18–0.26) across the size fractions.

In a study of filter effectiveness in an occupied townhouse, Wallace et al. (2004a) found for a mechanical filter that the increased coarse particle removal efficiency ranged from 60% to 80% while the efficiency for fine particle removal was near zero throughout the study. The improvement over time was attributed to particle accumulation on the filter, which increased the ability to trap other particles.

Wallace et al. (2004a) found that regular cleaning of an ESP was required to maintain performance. In that study, it was determined that cleaning of wires was important to remove a silicon-based molecule that deposits over time, perhaps from household use of deodorants or other products (Davidson and McKinney, 1998), as well as the cleaning of dust deposited on the collector plates.

14.1.7.2.4 Relationships between ambient levels and ambient/non-ambient components of indoor and personal exposure levels

In a review of the literature up to 2002, the US EPA 2004 PM AQCD concluded that various personal exposure studies had found that non-ambient PM exposure is independent of ambient PM concentration but that ambient PM exposure is a function of ambient PM concentration. The EPA assessment also concluded that ambient PM exposure, rather than total personal exposure, will have the stronger association with ambient PM concentration. Since the EPA report was issued, other research has been published to strengthen these conclusions.

In this review, no studies were found that examined the longitudinal correlation of the ambient and non-ambient components of indoor levels with ambient concentrations. Wilson and Brauer (2006) have estimated the daily ambient and non-ambient components of personal exposure based on sulphate measurements, in a 1998 study of 16 non-smoking COPD subjects in Vancouver, BC (Ebelt et al., 2000; Wilson and Brauer, 2006). Figures 14.9a and 14.9b show the

regressions of (a) total personal exposure estimates vs. ambient concentrations and (b) ambient exposure estimates vs. ambient concentrations. The coefficient of determination (R^2) for the total exposure–ambient concentration regression (0.07) was much lower than for the ambient exposure–ambient concentration (0.62), showing how the inclusion of non-ambient exposures in the total personal exposure reduced the correlation of total personal exposure with ambient levels. The non-ambient exposure was independent of ambient levels ($R^2 = 2 \times 10^{-6}$) (Figure 14.9c).

In a study of 37 patients with hypertension or cardiac defibrillators in Research Triangle Park, NC, researchers found the ambient component of personal exposure was more highly correlated with ambient $PM_{2.5}$ concentrations than was the correlation between total personal exposure and ambient concentrations (Williams et al., 2003a). Two pooled regressions, of ambient federal reference method (FRM) $PM_{2.5}$ concentrations with total personal exposure to $PM_{2.5}$ and of outdoor (near home) $PM_{2.5}$ with total personal exposure, both had an R^2 of 0.16. In a subsequent publication, Wallace et al. (2006b) carried out a regression of the ambient component of personal exposure with the ambient FRM concentration; the mean R^2 was 0.60 with a range of from 0.19 to 0.88 (median 0.73). Slightly higher R^2 s were found when the authors regressed the ambient component on the outdoor concentrations just outside each home (mean 0.71, range 0.42–0.93, median 0.81).

No published studies were found that looked at the relationship between ambient and non-ambient components of exposure with ambient PM concentrations for either ultrafine or coarse PM size fractions.

14.1.7.3 Source Apportionment of Personal Exposure Samples

The primary goal of source apportionment studies is to quantify determinants of PM exposure based on the chemical composition of PM in personal exposure samples. In these studies, conservation of mass is assumed and statistical methods are applied to estimate the fraction of airborne particle mass originating from various sources based on known or suspected chemical markers for each source (Hopke et al., 2006). When the number and composition of sources in a region are known, the contribution of each source to personal PM exposure can be estimated using regression methods such as the chemical mass balance model (Chow and Watson, 2002). However, when sources and their respective compositions are not known with certainty, statistical methods such as principal component/factor analysis and positive matrix factorization must be applied. In principal component/factor analysis, a new set of variables or “factors” are identified as linear combinations of the components measured in PM (e.g. trace elements, EC, OC) so that the variation in the data can be explained by a smaller number of variables (Hopke et al., 2006). Similar factors are also identified by positive matrix factorization, but the statistical method this procedure employs does not allow negative values (hence the name) and accounts for uncertainty in PM component measures owing to sampling error, outliers, detection limits, and/or missing data (Larson et al., 2004; Brinkman et al., 2006). In general, source profiles are selected based on literature data describing the chemical composition of PM that originates from common sources such as traffic emissions, vegetative burning, crustal materials, and regional air pollution (Cyrys et al., 2003b; Hopke et al., 2003; Lewis C et al. 2003; Koistinen et al., 2004; Kim D et al., 2005).

Source apportionment studies of personal PM exposure are summarized in Table 14.3. In total, seven source apportionment studies were identified that focused on characterizing sources of personal $PM_{2.5}$ exposures (Yakovleva et al., 1999; Oglesby et al., 2000; Hopke et al., 2003; Koistinen et al., 2004; Larson et al., 2004; Kim D et al., 2005; Zhao et al., 2006). Traffic combustion/mobile sources, secondary sulphate/regional air pollution, and crustal materials

Figure 14.9a Total PM_{2.5} personal exposure vs. ambient PM_{2.5} for 16 COPD subjects in Vancouver (Source: Wilson and Brauer, 2006)

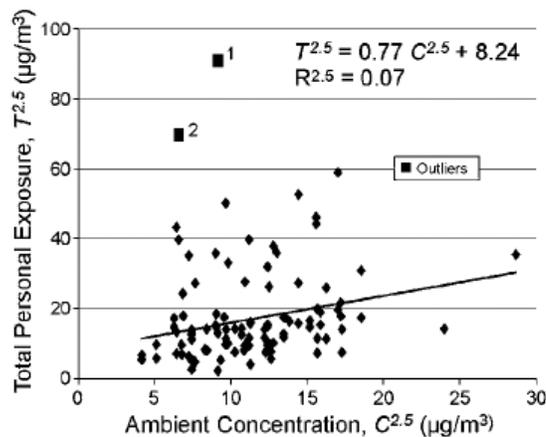


Figure 14.9b Ambient component of PM_{2.5} personal exposure vs. ambient PM_{2.5} for 16 COPD subjects in Vancouver (Source: Wilson and Brauer, 2006)

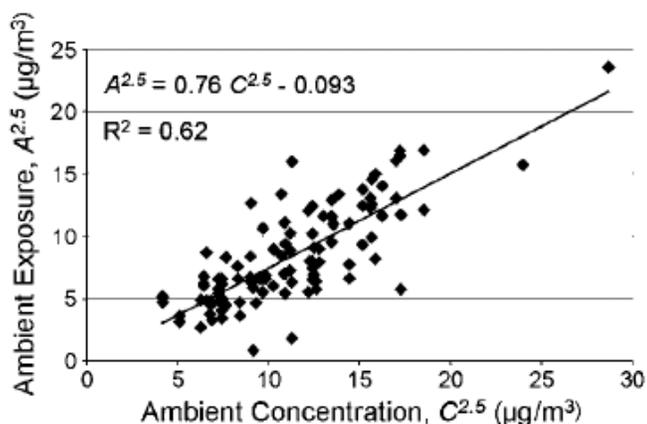


Figure 14.9c Non-ambient component of PM_{2.5} personal exposure vs. ambient PM_{2.5} for 16 COPD subjects in Vancouver (Source: Wilson and Brauer, 2006)

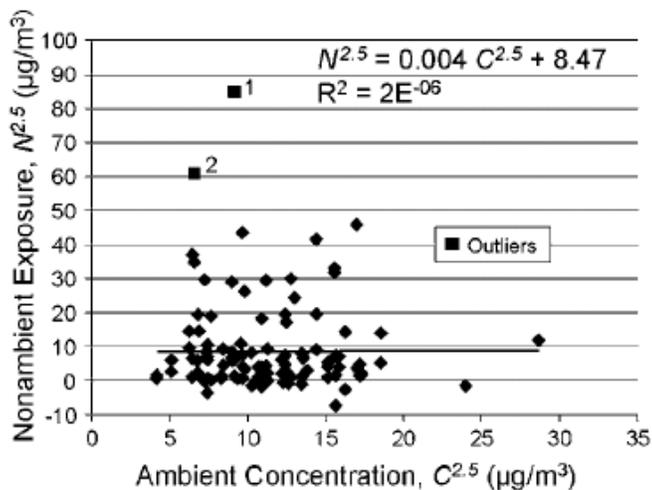


Table 14.3 Source apportionment studies

Source apportionment studies		
Toronto, ON Aug 1999–Nov 2001, 24-h samples Kim et al. (2005)	<i>Thermal/optical analysis (NIOSH method), FASS, and ion chromatography</i>	
	No. samples	259 (184 for EC)
28 heart disease patients 49–80 years of age, 5–10 measures/person	PM _{2.5} sources investigated and percentage contribution to PM exposure	<i>Traffic combustion: 13% Regional air pollution: 17% Crustal materials: 7%</i>
	<i>Thermal/optical analysis, XRF, ion chromatography</i>	
Baltimore, MD July–Aug 1998, 24-h samples Hopke et al. (2003)	No. samples	10
	PM _{2.5} sources investigated and percentage contribution to PM exposure	<i>Regional sulphate: 46% Soil: 3% Gypsum: <1% Personal care products: <1%</i>
Chapel Hill/Raleigh, NC June 2000–May 2001, 24-h samples Zhao et al. (2006)	<i>Thermal/optical analysis and XRF</i>	
	No. samples	266
38 adults with hypertension or cardiac defibrillators mean age 33 years, 7 measures/person	PM _{2.5} sources investigated and percentage contribution to PM exposure	<i>Cooking: 52.5% Secondary sulphate: 15.9% Motor vehicle emissions: 10% Other sources: <10%</i>
	<i>Thermal/optical analysis and XRF</i>	
Seattle, WA Sept 2000–May 2001, 24-h samples Larson et al. (2004)	No. samples	83
	PM _{2.5} sources investigated and percentage contribution to PM exposure	<i>Vegetative burning: 41% Crustal materials: 33% Secondary sulphate: 19% Mobile sources: 7%</i>
Helsinki, Finland Dates not provided, 48-h samples Koistinen et al. (2004)	<i>Analysis by XRF</i>	
	No. samples	76
76 adults 22–55 years of age, 1 measure/subject	PM _{2.5} sources investigated and percentage contribution to PM exposure	<i>Secondary sulphate: 31% Soil: 27% Detergents: 6% Sea salt: 2%</i>
	<i>Analysis by XRF</i>	
Riverside, CA Sept–Nov 1991, 12-h samples Yakovleva et al. (1999)	No. samples	356
	PM ₁₀ sources investigated and percentage contribution to PM exposure	<i>Soil: 17% Nonferrous metal operations/ motor vehicle exhaust: 22% Secondary sulphate: 21% Personal activities: 58%</i>

were the most common sources identified, but other factors such as vegetative burning, cleaning agents/personal care products, and cooking were also noted. Across studies the contribution of motor vehicle emissions ranged from 7% to 13%, crustal materials from 3% to 33%, and regional sulphate from 4.3% to 46% (Oglesby et al., 2000; Hopke et al., 2003; Koistinen et al., 2004; Larson et al., 2004; Kim D et al., 2005; Zhao et al., 2006). Cooking emissions contributed 52.5–54.8% of personal PM_{2.5} exposures in two studies (Yakovleva et al., 1999; Zhao et al., 2006), but factors such as sea salt, gypsum, and cleaning agents/personal care products generally contributed little to personal PM_{2.5} exposures (Hopke et al., 2003; Koistinen et al., 2004; Zhao et al., 2006). In three studies, a considerable portion (14–63%) of total PM_{2.5} exposure was not attributed to the ambient sources identified (Hopke et al., 2003; Koistinen et al., 2004; Kim D et al., 2005), perhaps owing to indoor sources. In general, however, little justification is provided in these studies for the naming of sources; in most cases, the attribution is based on literature data and not on source characteristic measurements collected within the specific region/population under investigation.

Under “personal activities,” Yakovleva et al. (1999) specifically described further breakdowns of categories corresponding to smoking, cooking, and vacuuming. The Yakovleva and the Zhao papers put proper emphasis on cooking as a major source. Perhaps because of the lack of source profiles for cooking, other studies often do not report a quantitative estimate of the cooking contribution (e.g. Kim D et al. (2005), with 63% of PM exposure unexplained). From the ambient/non-ambient studies, most of which show roughly comparable contributions from each, there should be major fractions of these source apportionments attributable to cooking and other indoor sources.

14.1.8 Exposure Measurement Error Issues in PM Epidemiology

Most epidemiological evidence concerning the health effects of PM, specifically PM_{2.5} and PM₁₀, comes from two types of studies: time-series studies relating daily mortality and morbidity to short-term fluctuations in PM, and cohort studies of the long-term (chronic) effects of sustained exposure to elevated levels of PM. In both types of studies, the average of measurements from one or more ambient monitors is used as a proxy for the population-averaged personal exposure to ambient PM in a specific geographic area. A number of authors have looked at the implications of using ambient monitoring data in these studies to determine what this exposure metric is representing and identify sources of measurement error. They have also examined how risk estimates from studies using ambient levels as the exposure metric relate to risk estimates between health effects and true levels of personal exposure to ambient PM (Zeger et al., 2000; Dominici et al., 2000; Wilson et al., 2000; US EPA, 2004; Sheppard et al., 2005).

A key issue is whether ambient levels from central site monitors are appropriate surrogates for personal exposure to ambient PM (rather than total personal exposure). In a review of the literature up to 2002, the US EPA 2004 PM AQCD concluded that ambient PM exposure, rather than total personal exposure, will have the stronger association with ambient PM concentration. The report also concluded that various personal exposure studies had found that ambient PM exposure is a function of ambient PM concentration. This finding has also been supported by more recent work discussed in Section 14.1.7.2.4. The 2004 assessment also concluded that non-ambient PM exposure is independent of ambient PM concentration, a finding also recently supported by Wilson and Brauer (2006). The EPA concluded that non-ambient exposure was not expected to contribute to the RR determined in a regression of health responses on ambient PM concentration, and hence could not be a confounder to the ambient PM–health effects relationship. However, it was noted that non-ambient PM could raise the overall exposure level and contribute to the observed health effects, making it more difficult to observe a threshold

level for ambient PM. In a more recent publication, Sheppard et al. (2005) carried out a simulation study looking at the impact of varying non-ambient exposure distributions on risk estimates obtained from a time-series study, based on data collected in Seattle, WA. The simulation showed that when ambient and non-ambient exposures are independent, changes in the distribution of the non-ambient exposure have no impact on the health effect parameter estimate for the ecologic time-series design. Additional simulations with nonzero correlations did not show notable evidence of specification bias, likely because of the near linearity of the health effect in the situation.

A number of papers have identified and evaluated key sources of measurement error (Zeger et al., 2000; Carrothers and Evans, 2000; Dominici et al., 2000; Sheppard et al., 2005; Wilson et al., 2005). One source is the difference between the actual and measured average ambient levels in a community. This difference may arise from measurement error in the sampling device, which may be completely random, or may involve bias if the device systematically underestimates or overestimates the ambient PM concentration. Random unbiased measurement error can be compensated for by averaging measurements from multiple devices. Device bias may be avoided by using measurements that have been collected from instruments that conform to FRM standards, or are calibrated to FRM instruments and have been collected with appropriate quality assurance methods. Measurement error may also occur if the monitor(s) is/are not located so as to reflect the spatially averaged ambient levels in the community, which could introduce bias in the risk estimate.

The second source of measurement error comes from the difference between a specific person's exposure to ambient-generated PM and the mean population exposure to ambient PM; this reflects spatial variability in ambient levels and where people spend their time, as well as variability across buildings in building infiltration rates and variability across individuals in time-activity patterns (Carrothers and Evans, 2000). PM_{2.5} generally has less spatial variability than PM₁₀ or coarse particles, but in a recent review of the literature Wilson et al. (2005) found that 43% of the reviewed PM_{2.5} studies reported heterogeneous PM_{2.5} levels (compared with 60% for PM₁₀). Wilson et al. (2005) point out that within-community variation is not likely to be a source of large error in risk estimates if temporal correlation between sites is high, and that any bias is likely to lead to underestimation of the health risk estimates. Other authors have also concluded that having aggregate rather than individual exposure does not lead to bias in the regression coefficient in longitudinal (time-series) studies; however, it will lead to more uncertainty in the risk estimates (Carrothers and Evans, 2000; Zeger et al., 2000; Meng et al., 2005b). Similarly, in a cohort study, different levels of between-individual variability in different cities should not introduce bias but will increase uncertainty in the risk estimates.

The third source of measurement error is the difference between population-average personal exposures to ambient PM and the mean ambient PM concentration at one or more central sites. Health effect estimates based on fixed ambient PM monitoring data will be different from those obtained when using personal exposures to ambient PM. However, when the ambient levels are correlated with community-averaged personal exposures to ambient PM over time, the health effect estimate obtained when using ambient levels, β_x , is related to the health effect estimate obtained when using personal exposure to ambient PM, $\beta_z = \alpha \beta_x$, where α is a factor that defines the relationship between the two exposure metrics (Zeger et al., 2000; Dominici et al., 2000). (From a regulatory perspective, it may be that β_z is the parameter of greater interest, since it describes the change in risk associated with changes in ambient levels). In the exposure measurement literature, many authors refer to α as the "attenuation factor"—it is the same as F_{pex} described earlier in this document. If the attenuation factor varies across communities (due to differences in building structures, use of A/C or open windows, and time spent outdoors), estimates of risk will vary across cities.

If the mean attenuation factor is correlated with the mean ambient concentration, which might occur if there are seasonal variations in the attenuation factor due to seasonal variations in particle infiltration (F_{inf}), then the risk estimate in time-series studies may be biased (Meng et al., 2005b). Since ambient levels and mortality and morbidity may also vary on a seasonal basis, the bias can be in either direction. Sheppard et al. (2005) carried out a simulation study based on exposure data from Seattle, WA, looking at the effect of a range of variants in the PM distribution on the health effect parameters in a time-series study. In the simulation, the population distribution of attenuation factors was constrained to be low in the winter with progressively larger seasonal variation (Sheppard et al., 2005). The result was an estimate of the risk factor that was biased low with greater bias as the seasonal structure increased. Similarly, when the attenuation factor was higher in the winter, the risk estimate was biased high with increasingly more bias with the highest seasonal structure. The authors concluded that variation in individual attenuation factors (i.e. F_{pex} s) only matters in time-series studies to the degree that it is temporally correlated with ambient concentration. As mentioned, health effect studies have generally used ambient $PM_{2.5}$ or PM_{10} as the exposure measure. In fact, PM is a complex mixture of varying size, composition and relative toxicity. Issues of measurement error for other particle sizes, such as UFPs, coarse PM or PM components have not been investigated as thoroughly. Both UFPs and coarse PM and many $PM_{2.5}/PM_{10}$ components are known to have higher spatial variability than $PM_{2.5}$ (Martuzevicius et al., 2004 (components); Kim D et al., 2005 (components); Sioutas et al., 2005 (UFPs)). For example UFPs, associated with combustion sources such as traffic, have been shown to decrease exponentially with distance from a major roadway (Levy et al., 2003; Zhu et al., 2002a, 2002b, 2006). Westerdahl et al. (2005) found that urban background UFP concentrations in Los Angeles, CA, differed by at least an order of magnitude from the levels on a freeway. Increased spatial variability should not bias the risk estimates but rather increase their uncertainty, making it harder to detect a significant association between exposure and health effects. If exposure to these size fractions and components involves activities that are related to other morbidity/mortality risk factors, such as working close to traffic, then measurement error could lead to underestimated risks.

Infiltration rates are very dependent on particle size and composition, as discussed in Section 14.1.7.2.3, with AMPs having the greater infiltration rate. Sarnat et al. (2006b) found the lowest infiltration rate for volatile species and concluded that particle composition likely influences observed epidemiological relationships based on outdoor PM concentration, especially in areas with elevated levels of NH_4NO_3 and/or other volatile particles. Similar concentrations of PM mixtures may well lead to substantially different exposure to the more toxic components. Consequently, similar exposure levels might lead to different levels of risk.

A number of pollutants such as ozone, nitrogen dioxide (NO_2), and CO are correlated with ambient PM concentrations and also associated with changes in mortality and morbidity. Models exploring the effects of individual pollutants often attempt to control for the effects of confounding co-pollutants by including them in the model as additional covariates. This can potentially be problematic when different pollution concentrations are measured with different degrees of accuracy. If two pollutants are highly correlated, the risk coefficient for the pollutant measured with greater precision will be biased upwards and the risk coefficient for the pollutant measured with lower precision will be biased downwards (Zidek et al., 1996; Carrothers and Evans, 2000; Zeka and Schwartz, 2004). Changes in the sign of a coefficient can occur only when the measurement errors for different pollutants are highly correlated with one another (Zeger et al., 2000). Seasonal differences in the measurement error of gaseous co-pollutants can lead to bias in multi-pollutant models. Depending on the correlational and measurement error structure, the bias can be either upward or downward. Koutrakis et al. (2005) examined these issues in a simulation study that generated a distribution of health effect estimates for pollutants when the measurement errors and cross-pollutant correlations matched those

observed in an earlier study in Baltimore, MD. Simulations were carried out for a variety of assumed true health effect associations with exposures to each of the pollutants. Personal exposure to PM_{2.5} of ambient origin was assumed to be truly associated with an adverse health risk with a true coefficient of 0.05. In the simulations, ambient PM_{2.5} concentrations were found to be associated with the health outcome; the beta coefficient was 0.018, representing an attenuation of 60%. The simulation also found that a true association with PM_{2.5} would result in a significant, observed association with ambient NO₂.

A number of authors have identified the need for a better understanding of the nature of exposure measurement errors that could affect the findings of PM epidemiological studies. They call for a better understanding of factors affecting the temporal and spatial variability of the attenuation factor (Meng et al., 2005b), changes in the composition of ambient PM_{2.5} with outdoor to indoor transport (Meng et al., 2005a), the covariance structure of various co-pollutants and co-factors affecting spatial variability in various areas and for various PM components and size fractions, and whether and how the attenuation factor co-varies with ambient levels in different geographical areas (Sheppard et al., 2005).

Some innovative and improved exposure metrics have been used in recent epidemiological studies. Strand et al. (2006) has used regression calibration to adjust the pollutant slope estimate β_z using an estimate of the attenuation factor based on the personal/outdoor sulphate ratio to gauge the actual risk estimate β_x . In two small panel studies, the ambient and non-ambient components of personal exposure were estimated separately for each participant. In a study of 16 COPD patients, Ebel et al. (2005) found the cardiopulmonary outcomes were significantly associated with the ambient component of exposure but not with the total exposure or the non-ambient component. Similarly, in a study of 19 asthmatic children, Koenig et al. (2005) observed that the ambient component of exposure, but not the non-ambient component, was significantly associated with an increase in exhaled NO in participants who were not using corticosteroid therapy. As well, a number of studies have looked at the association of various health outcomes with specific PM components (e.g. Sørensen et al., 2005a; Perera et al., 2006 (PAHs); Delfino et al., 2006 (EC, OC)) and with estimates of source-specific PM, derived using techniques such as source apportionment (e.g. Penttinen et al., 2006; Mar et al., 2006; Hopke et al., 2006).

14.1.9 Summary and Considerations: Exposure Assessment

Total personal exposure to PM consists of exposure to ambient PM and to indoor-generated (non-ambient) PM. This document focuses on Canadians' exposure to ambient PM, which is a function of ambient PM levels, time spent outdoors and levels and factors affecting infiltration of ambient PM into indoor environments. Most of the literature pertains to PM_{2.5} and to a lesser extent PM₁₀, with much less data available for coarse PM, UFPs, or PM components such as EC, elements, metals, ions, and organic components such as PAHs.

Ambient levels of PM_{2.5} and PM₁₀ in Canada are available from the NAPS dichot and TEOM monitor networks. Southern Ontario and southern Quebec continue to record the highest PM_{2.5} levels in Canada, as defined by the form of the CWS. Almost all monitoring sites over the CWS 2010 targets are located in these regions, although PM_{2.5} levels are closer to the target than is the case for ozone. These regions also have the highest number of days and frequency of episodes with levels greater than the CWS numeric target of 30 µg/m³ for PM_{2.5}, although these events are observed with lesser frequency in other regions. The spatial pattern of PM_{2.5} across the country varies regionally and seasonally. Local ambient levels of PM_{2.5} are influenced by a variety of factors that can lead to substantial differences in ambient concentrations from one region of the country to another over time. These include meteorology, natural emissions,

coastal and urban effects, the local chemical mixture, transboundary transport and background concentrations. High PM_{2.5} levels occur both in summer and winter, with the cold season receiving more attention recently due to the more significant role of local emission sources and primary pollutants (e.g. primary PM_{2.5}) than in the summer.

Four studies have directly measured total personal exposure levels to PM_{2.5} in Canada. A large population-based study measured levels in Toronto, ON, in 1995/96 and found that the median PM_{2.5} personal exposure for non-smokers was 17 µg/m³, compared with the median ambient level of 15 µg/m³. Three other small panel studies involving <20 non-smoking participants each (children in Prince George, BC, persons with CVD in Toronto and COPD in Vancouver, BC) found median levels ranging from 14 to 16 µg/m³ with considerable variability in day-to-day levels (maximums ranging from 91 to 503 µg/m³). The median ambient levels in these studies ranged from 9 to 14 µg/m³. The results from the Toronto and Prince George studies fall in the lower range of levels reported from other studies in the US and Europe of healthy adults/general population and healthy children, respectively. The median levels reported in the Vancouver and Toronto studies fall in the middle of the range of median personal exposures reported from other panel studies of health-compromised participants. There appears to be a general trend for lower exposure levels in studies of healthy elderly, and children and adults with pre-existing disease conditions; however this is difficult to confirm, given the lack of general population studies in the same communities for comparison. It has been hypothesized that some individuals with disease conditions who spend less time in outdoor environments, and those living in institutional residences with mechanical filtration systems, may have lower exposure to ambient PM. In healthy individuals, non-ambient exposures are more variable and can dominate personal exposures (compared with ambient exposures), obscuring relationships between total personal exposures and ambient levels.

Few studies have measured personal exposure to ultrafine PM, due to the lack of sampling equipment suitable for personal sampling. UFP exposures appear to be significantly higher in traffic microenvironments, such as near roadside or in-vehicle, or other locations close to combustion sources. As well, few studies have been carried out looking at personal exposure to PM components, such as EC/OC, trace elements and ions or PAHs. Two small studies conducted in Toronto and Prince George each observed lower personal EC exposures than those reported for other geographic locations. Outdoor sources such as vehicle traffic appear to be an important determinant of personal EC exposures, and EC appears to be a better marker of vehicle traffic than PM_{2.5}. Transition metals and ions such as sulphate and nitrate are associated with PM originating mainly from industrial sources and fuel combustion. Vehicle exhaust and charcoal burning have been identified as ambient sources of PAHs. The small number of studies conducted to date make it difficult to determine whether specific population subgroups have different exposures to these elements; for many components, with sulphur being the notable exception because of its few indoor sources, it is difficult to separate the ambient and non-ambient sources when looking at personal exposure samples.

Different individuals and populations may be more exposed to PM of ambient origin due to their time-activity patterns, building characteristics, ventilation and other factors that affect infiltration. Time-activity studies of the general population from Canada and the US have consistently found that people spend a majority of time indoors (87–89%), mostly at home. In a Canadian time-activity study, the average time spent outdoors ranged from 5% to 10% across age groups and time spent in-vehicle ranged from 3% to 6%. By comparison, it appears that children spend slightly more time indoors away from home, whereas elderly and compromised subjects spend more time indoors at home. Time spent in transit and indoors at work or school followed a decreasing gradient across groups of adults, children and the elderly (with or without a pre-

existing disease). Individuals spending more time outdoors will be exposed to more ambient PM. Commuters spending time in heavy traffic will have more exposure to UFPs.

The infiltration factor (F_{inf}) is the proportion of ambient PM that penetrates a building and stays suspended; a number of methods are described for estimating F_{inf} . Few Canadian data are currently available; however, there are a number of $PM_{2.5}$ studies from the US and Europe. Across studies, the average $PM_{2.5}$ F_{inf} ranged from 0.3 in Minneapolis/St. Paul, MN, to 0.82 in Athens, Greece. Most studies have estimated an average F_{inf} across homes; in cases where F_{inf} has been estimated in individual homes, considerable between-home variability was reported.

PM infiltration is strongly dependent on particle size, due to its effects on the deposition rate and penetration factor. AMPs (0.1–1.0 μm), which make up the bulk of $PM_{2.5}$ mass, have higher F_{inf} , while ultrafine and coarse particles have the lowest F_{inf} . Infiltration factors for various PM components, such as EC, sulphur or metals, depend largely on particle size and volatility.

PM infiltration is strongly associated with AERs for particles of all sizes; hence particle infiltration is related to building construction (i.e. building tightness) as well as season and occupant behaviours that affect AERs, particularly the use of open windows and doors, A/C, mechanical ventilation and filtration systems. It appears that F_{inf} increases rapidly as AERs rise to about 0.55/h and then increases more gradually to a plateau around 0.8–1.0 when the AER is above 1.5/h. AERs are typically associated with season; they increase with open window use and decrease with closed windows, during the heating season and periods of A/C. As well, the tighter house construction typically used in newer houses and in colder climates leads to lower AERs (when the windows are kept closed). It is expected that infiltration factors in Canada in the winter may be lower than elsewhere, particularly in locations where the building structures are built relatively tight because of the cold winter climate. In other seasons when open windows are more prevalent it is expected that infiltration rates would be considerably higher. In summer, in areas where A/C is more prevalent, it is expected that infiltration rates would be lower.

PM filtration devices can be effective at reducing particle levels in homes or office buildings. Generally, electrostatic precipitators and HEPA filters are the most effective systems, while standard furnace filters are relatively ineffective. Filters are generally best at collecting the smallest (ultrafine) and largest (coarse) particles, with minimum efficiencies for particles in the range of 0.2–0.4 μm .

The personal exposure factor (F_{pex}) is the proportion of ambient PM to which a person is exposed. Mean $PM_{2.5}$ F_{pex} s across various studies from Canada, the US and Europe ranged from 0.15 to 0.79, with considerable individual variability found in all studies that estimated F_{pex} for each participant. Three small Canadian studies of health-compromised participants (St. John, Toronto and Vancouver) have estimated mean F_{pex} s ranging from 0.60 to 0.75. Two of them estimated F_{pex} for each individual and also found large variability in F_{pex} across individuals. Few data are available regarding F_{pex} for coarse or ultrafine particles. The Vancouver COPD study estimated a mean F_{pex} for $PM_{10-2.5}$ of 0.41, lower than the 0.71 for $PM_{2.5}$, as would be expected due to the reduced infiltration efficiency of coarse PM.

A number of studies also estimated the ambient and non-ambient components of personal $PM_{2.5}$ exposure; again, some estimated means across the participants and some the components for each participant. The estimated mean ambient components of personal exposure from two of the Canadian studies mentioned above and an additional modelling study were 8.25 $\mu g/m^3$ (Toronto CVD study), 8.1 $\mu g/m^3$ (Vancouver COPD study) and 8.0 $\mu g/m^3$ (Toronto general population model), respectively.

Some studies found higher ambient components of personal exposure during the summer, compared with fall or winter, presumably due to higher infiltration rates with more open windows

and doors, and perhaps more time spent outdoors. There is no apparent evidence of large differences in the mean $PM_{2.5} F_{pex}$ between the various population subgroups, but the number of studies carried out to date is limited. Similarly, there are no apparent differences in the mean ambient component of personal $PM_{2.5}$ exposure across various study groups. There is some evidence that the non-ambient component of personal exposure is higher in studies of the general population than in other health-compromised subpopulations; however the dataset is very limited, making it difficult to draw any firm conclusions.

The US EPA 2004 PM AQCD concluded that ambient PM exposure was a function of ambient PM concentration but that non-ambient PM exposure was generally independent of ambient PM concentration. It stated that ambient PM levels were a suitable surrogate for personal exposure to ambient PM in epidemiological studies. Since then, further studies have strengthened these conclusions for $PM_{2.5}$; however, few data are available for either the ultrafine or coarse PM size fractions. A number of authors have looked at the implications of using ambient monitoring data in PM epidemiological time-series and cohort studies to determine what this exposure metric is representing, to identify sources of measurement error and to examine how risk estimates from studies using ambient levels relate to the risk estimates between health effects and levels of personal exposure to ambient PM. In general, non-ambient PM exposure is not expected to be a confounder to the risk estimate for ambient PM. Measurement error is reduced by averaging measurements from multiple devices and appropriately placing the monitors to reflect the spatially averaged ambient levels in a community. Variability across individuals in time-activity patterns and residential infiltration rates, as well as spatial variability in the ambient PM level will lead to more uncertainty in the risk estimates. This is more likely to be the case for ultrafine and coarse PM, which have higher spatial variability than $PM_{2.5}$. The health effect estimate based on using ambient PM monitoring data, rather than that obtained when using personal exposures to ambient PM, will be attenuated by the personal exposure factor (F_{pex}) (or attenuation factor), which depends on time spent outdoors and the infiltration factor. If the F_{pex} varies across cities due to differences in building structure, use of A/C or open windows and time spent outdoors, estimates of risk in time-series studies will vary across cities. If the mean F_{pex} is correlated with the mean ambient concentration, which might occur if there are seasonal variations in particle infiltration, then the risk estimates may be biased in either direction. Co-pollutant models that involve pollutants measured with varying degrees of precision can be subject to bias in the risk estimates. As well, seasonal differences in the measurement error of co-pollutants can lead to bias. Depending on the correlational and measurement error structure, the bias can be either upward or downward.

14.2 Dosimetry

14.2.1 Introduction

Dosimetry investigation plays a significant role in the characterization of exposure to ambient PM. Dosimetric information is important for understanding PM toxicity, including extrapolating effects found in toxicological studies of laboratory animals to those observed in humans, and for relating effects in healthy individuals to those in susceptible individuals. Retention of particles within the respiratory tract is governed by the balance between deposition and clearance processes. Deposition of inhaled particles in the respiratory tract is mainly influenced by the physical and chemical properties of the particles and the morphology and physiological status of the respiratory tract. After deposition onto the surfaces of the respiratory tract, particles are subjected to either absorptive or non-absorptive particulate clearance processes, which 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 the disposition of the particles to specific translocation pathways.

For dosimetric purposes the respiratory tract can be divided into three sections: extrathoracic (ET), tracheobronchial (TB), and alveolar (Figure 14.10) (Wang, 2005). The ET region is the area through which air first passes during inhalation and includes airways within nasal and oral passages to the larynx. In contrast to most experimental animals used in inhalation studies, which are obligatory nose-breathers, humans are oro-nasal breathers, able to breathe either through the nose, the mouth, or both airways simultaneously. Air enters through the ET region, and passes through the TB section of the respiratory tract via the trachea. The trachea bisects into two bronchi, which subsequently branch into smaller segments (airway generations) until the terminal bronchiolar region. The gas-exchange section at the end of the terminal bronchioles is referred to as the alveolar region, which is specifically composed of respiratory bronchioles, alveolar ducts, alveolar sacs and alveoli. All of the conducting airways, with the exception of the trachea and portions of the main stem bronchi, are surrounded by parenchymal tissue, while blood and lymphatic vessels irrigate alveolar structures (US EPA, 2004; Wang, 2005).

14.2.2 Types of Air Flow

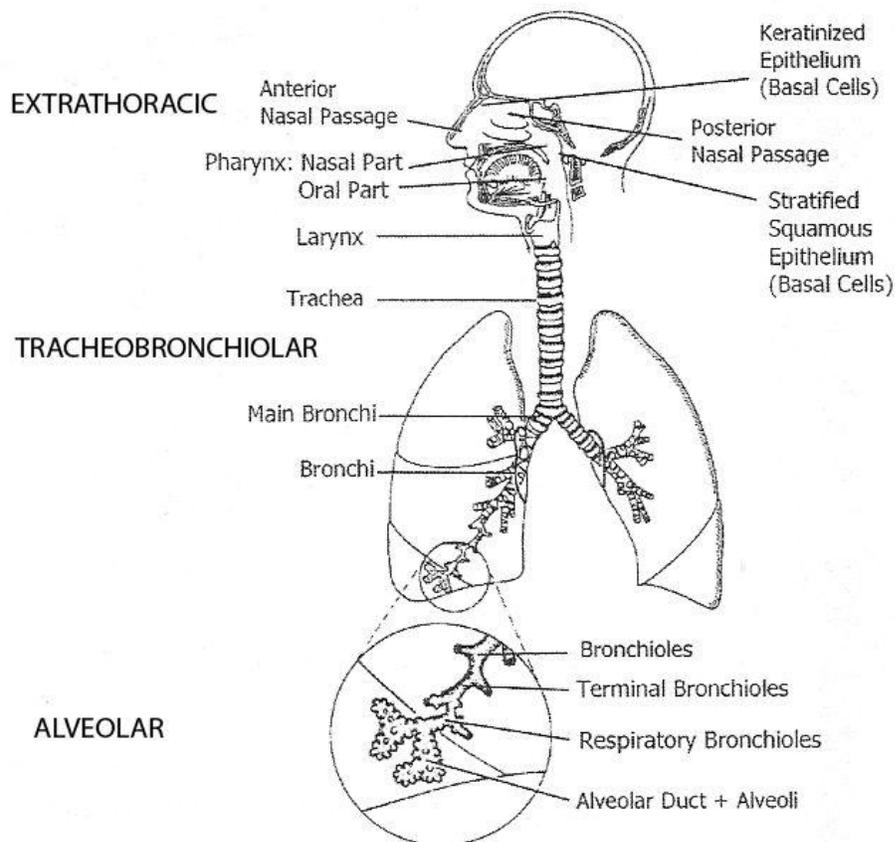
There are three major types of airflow in the respiratory tract: 1) laminar, 2) turbulent, and 3) transitional. These airflow patterns are influenced by the velocity of the air in the airway, the density of the gas, and the size and branching of the airway.

Laminar flow is characterized by streamlines of gas moving parallel to one another and the sides of the airflow tube; it prevails at low flow rates. Turbulent flow is characterized by a more random movement of gas along the tube, and prevails at high flow rates. Gas density is important in determining turbulent flow rates; an increase in density results in a decrease in flow rate. In addition, the driving pressure for turbulent flow is proportional to the square of flow rate. Transitional flow is characterized by eddies that form at tube bifurcation. Since the human respiratory tract is full of branches, transitional flow is an important flow pattern to consider in the lung (Grippi, 1995).

14.2.2.1 Reynolds Flow Rate

Whether flow through the respiratory system is turbulent or laminar can be predicted by calculating the Reynolds number (Re), a unitless value that relates mean velocity of flow to gas

Figure 14.10 The respiratory tract (from Wang, 2005)



density, gas viscosity, and tube radius. When Re exceeds 2000, flow is turbulent; when Re is less than 2000, flow is laminar.

14.2.3 Types of Particle Deposition

Particle deposition can be described by six general mechanisms: 1) inertial impaction, 2) sedimentation, 3) diffusion, 4) interception, 5) electrostatic precipitation, and 6) Brownian motion (US EPA, 2004; Isaacs and Martonen, 2005; Wang, 2005). The mechanism that comes into play for any given particle mixture is dependent upon the physical characteristics of the particles (most notably particle size, as well as their chemical composition, including charge and hygroscopic potential), but is also dependent upon the velocity and type of airflow in the airway.

Inertial impaction represents a significant deposition mechanism for particles larger than $2 \mu\text{m}$ aerodynamic equivalent diameter (AED) (US EPA, 2004). Inertial impaction is the process by which the inertia of the inhaled particle makes it unable to follow changes in airstream direction or air velocity streamlines (Asgharian et al., 2006). The particle will continue with its direction despite sudden changes in airway directions and will hit whatever surface it comes into contact with. This type of deposition characterizes the ET and upper region of the TB airways, and is typical of larger particles (Isaacs and Martonen, 2005).

Sedimentation or gravimetric deposition refers to the settling out of particles from the airstream due to gravitational forces (Asgharian et al., 2006), and affects all particle sizes, though those of an AED greater than 1 μm are most likely to be involved (US EPA, 2004). Both sedimentation and inertial impaction can influence the deposition of particles within the same size range; inertial impaction dominates in the upper airways, and gravitational settling becomes increasingly important in the smaller conducting airways (US EPA, 2004). In general, in the ET and upper TB regions, inertial impaction and sedimentation dominate, though other mechanisms such as fluid flow convection (Kojic and Tsuda, 2004), interception and oscillatory flow add complexity to these processes.

In contrast, diffusive deposition affects particles of less than 1 μm AED. Instead of being related to AED, diffusivity of smaller particles (<1 μm) of different shapes can be related to the thermodynamic equivalent size based on spherical particles (i.e. particles of that size or smaller collide with air molecules, resulting in contact with airway surfaces) (US EPA, 2004). Deposition of particles 0.2–1.0 μm in diameter is influenced by both gravitational and diffusive mechanisms, though the relative importance of these is dependent on the exact size within this range. Particles smaller than 0.1 μm in diameter are solely deposited due to diffusion (Heyder, 2004).

Brownian motion plays a role in diffusive deposition mechanisms (Asgharian et al., 2006). Brownian motion is the random movement of tiny particles suspended in a solution, in this case gas, due to collisions with other molecules in the solution. In an inhalation model, particles that are undergoing Brownian motion will strike other particles in the air, causing them to move about in the gas, without necessarily impacting the surrounding tissues. Often, because the particles do not hit airway walls, they will simply be exhaled due to their small size. Thus Brownian motion is something that needs to be considered in dosimetric analyses; however, it will not always result in increased tissue doses.

Electrostatic precipitation is mainly related to particle charge (ionization). The electrical charge on some particles will result in an enhanced deposition over what would be expected from size alone (US EPA, 2004) if the charge allows for particle interaction with the charged airway walls. The effect of charge on deposition is inversely proportional to particle size and airflow rate. This type of deposition is often of lesser importance than the effects of turbulence and other deposition mechanisms, and it generally has been considered to be a minor contributor to overall particle deposition (US EPA, 2004; Isaacs and Martonen, 2005).

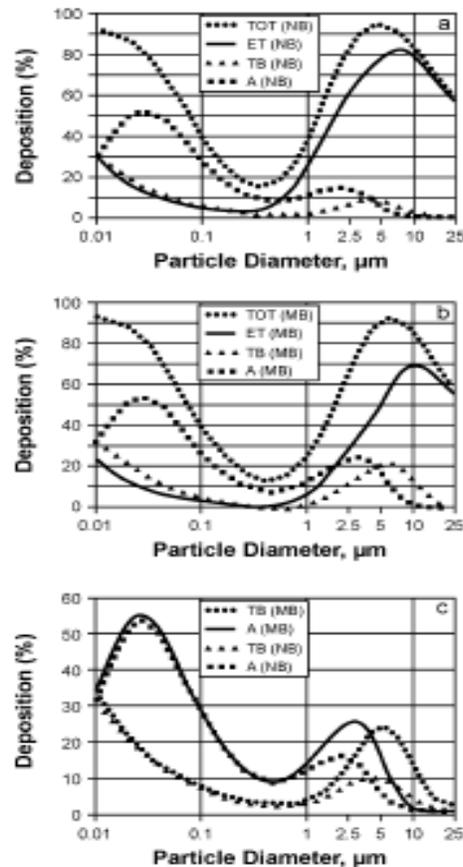
14.2.3.1 Particle Deposition in the Respiratory Tract by Particle Size

Particle deposition in the respiratory tract is largely determined by particle size, though breathing patterns play an important role. The experimental data and modelling efforts are very well developed for deposition of airborne PM. The information base for humans, some of which has been touched on in Section 14.2.3, is summarized in Figure 14.11 (from US EPA, 2004).

The figure summarizes deposition of PM in the respiratory tract of an adult worker with moderately high activity, as predicted by the International Commission on Radiological Protection (ICRP) model. It shows the predicted total and regional deposition as a function of particle size for (a) nasal breathing, (b) mouth breathing, and (c) a comparison of nasal and mouth breathing for the TB and alveolar regions. For all regions, the deposition is at a minimum between 0.1 and 1 μm (the accumulation mode size range), and increases for coarse and ultrafine size ranges. For UFPs, alveolar deposition is greatest between 0.01 and 0.1 μm and TB and ET deposition each increase at particle sizes below 0.1 μm . For coarse PM, deposition peaks at round 10 μm in the ET region, and in lesser amounts and at smaller particle sizes in the TB and alveolar regions. Nasal and mouth breathing show little or no difference in

deposition for ultrafine and accumulation mode particles, but breathing through the mouth results in greater TB and alveolar deposition of coarse particles as a result of bypassing the nose (which captures coarse particles very efficiently).

Figure 14.11 Deposition fraction for total results of LUDEP model for an adult male worker (ICRP default breathing parameters) showing total percentage of deposition in the respiratory tracts (TOT) and in the ET, TB, and alveolar (A) regions: (a) nasal breathing (NB), (b) mouth breathing (MB), (c) comparison of nasal and mouth breathing for TB and A regions.



14.2.3.2 Hygroscopic Changes to Particle Size

Particle hygroscopicity plays a role in deposition of certain ambient particles, as it will increase the particle size by the addition of water molecules to the particle. Fine particles such as sulphates, nitrates and possibly organic PM can take up and retain moisture; thus they can increase in size in the humid air of the respiratory tract. This phenomenon results in particles depositing within the respiratory tract in accordance with their new hydrated size rather than with their original ambient size (US EPA, 2004; Heyder, 2004).

14.2.4 Biological Factors Affecting Particle Deposition

14.2.4.1 Minute Volume, Tidal Volume and Respiratory Rate

Respiratory minute volume is the volume of air inhaled or exhaled from a person's lungs in one minute. Minute volume is calculated by taking the tidal volume (the lung volume representing the normal volume of air displaced between normal inspiration and expiration when extra effort is not applied) and multiplying it by the respiratory rate (the number of breaths per minute a person is taking). Alternately, it can be calculated by the sum of alveolar ventilation (the volume of gas per unit time that reaches the alveoli) and dead space ventilation (the volume of gas per unit time that does not reach these respiratory portions, but instead remains in the airways).

Both minute volume and tidal volume are related to lung capacity. Lung capacity is related to lung size (correlated to body size, and therefore related to gender and age) and to lung health (occlusions or changes to pulmonary elasticity/function will decrease lung capacity).

14.2.4.2 Differences in Biological Factors

Investigations on particle respiratory tract deposition usually consider healthy adult Caucasian subjects. However, changes in lung capacity, airway size or breathing rate related to gender, activity, age, respiratory disease or interindividual anatomical differences can greatly modify particle deposition within the respiratory tract.

14.2.4.2.1 Gender

Anatomical differences between genders (such as body and airway size) and variation in ventilation dynamics may result in differences in PM dosimetry between women and men. Not all studies account for gender differences, which may explain the contrasting results reported in the scientific literature for PM dosimetry.

The US EPA 2004 PM AQCD reviewed studies on this topic and reported that, in general, women exhibit greater proximal (shallower) fractional deposition of particles than men (though the absolute deposition rate can be greater in males during spontaneous breathing because of a greater ventilation rate in males). Overall, the gender effect appeared particle-size dependent, with greater fractional deposition in females for very small ultrafine and large coarse particles, but not for particles ranging from 0.08 to 0.1 μm (US EPA, 2004). Kim and Jaques (2004) conducted a study in which men and women were exposed by inhalation to inert UFPs with Number Median Diameters (NMDs) of 0.04, 0.06, 0.08 and 0.10 μm ; they showed comparable total respiratory tract deposition fraction (TDFs), though women exhibited a trend towards higher TDFs for the smaller-size particles tested (0.04 μm), consistent with earlier findings for UFPs. Chalupa et al. (2004) conversely reported a lack of gender differences of TDFs in men and women administered carbon UFPs. Differences in lung anatomy related to smaller dimensions of the upper airways have been postulated as the explanation for some of these findings. However, experimental conditions may also play a role. Changes to normal female breathing patterns under experimental conditions that do not distinguish between male and female lung capacity may account for these differences, or lack thereof. Women might experience increased minute ventilation (compared with their normal ventilation) when forced to breathe at the same tidal volume and frequency as men. Experimental procedures when dealing with male and female subjects are, therefore, an important consideration for dosimetric and exposure analysis.

14.2.4.2.2 Activity patterns and physical exercise

Studies reviewed in the US EPA 2004 AQCD and more recently have provided evidence that for all particle sizes, even moderate exercise can elicit 3–5 times greater total lung deposition rate (i.e. deposition per unit time) than occurs at rest (Daigle et al., 2003; Chalupa et al, 2004; CIIT, 2005). Factors that enhance total and local deposition of inhaled particles during physical

exercise include higher minute ventilation than when at rest, and greater prevalence of oral breathing (which bypasses the filtering efficiency of the nose).

Voutilainen et al. (2004) used deposition probability functions obtained from the computerized ICRP 66 deposition model (ICRP, 1994) to model the numbers and masses of particles depositing in the respiratory tract against actual occurrence in one male adult. The man's physical activity and minute ventilation during the day were taken into account in the calculations. This study reported a much higher number and mass of deposited particles in the respiratory tract during the day (7 a.m. to 7 p.m.) than during the night (7 p.m. to 7 a.m.). These results are explained by the daily variation in the number and size mass distribution of aerosols in the air, and the physical activity and rest patterns of the individuals.

14.2.4.2.3 Age

Age, which coincides with variations in airway size and physiology, plays an indirect role in the lung deposition patterns of inhaled particles. Scientific literature describing the association between particle deposition efficiency and age appears to indicate that children, particularly infants, may be at a greater health risk from exposure to airborne PM and noxious materials, if all other conditions remain equal. The US EPA 2004 AQCD presented a review of this topic wherein experimental results provided equivocal evidence of greater deposition in children vs. adults, but noted that significant differences in activity patterns may explain the greater overall deposition in children. They reported similar results from modelling efforts designed to understand potential differences in deposition between children and adults. In virtually all the studies evaluated by the EPA, deposition in children was greater than in adults, with some evidence of greater upper airway deposition (i.e. in the ET and TB regions). Children also generally received greater doses of particles per lung surface area than adults (US EPA, 2004). Kim and Jaques (2005) found that in healthy elderly adults, deposition characteristics did not appear markedly different from those in young adults

A study by Asgharian and Price (2004) used a multiple-path particle deposition model to calculate particle deposition fractions in different regions of the lung lobes and airway generations of children and adults between the ages of 3 months and 21 years. The particle sizes tested ranged from 0.01 to 10 μm in diameter. The study showed larger nasal deposition in adults than in children under breathing rates simulating breathing at rest. However, after adjusting for inhaled air lung volume by taking into account the direct proportionality between deposition fraction in a lobe and the volume of air entering that lobe, infants showed the greatest TB and pulmonary deposition fractions. The deposition fraction decreased with age. This effect is partially explained by Corcoran et al. (2004), who characterized airflow in children using computational fluid dynamics (CFD) techniques to simulate airflow in an *in vitro* model of the pediatric upper airways. In comparison to adult airway models, the convective effects of the laryngeal jet in pediatric subjects were amplified (high mainstream and reverse axial velocities, elevated turbulent kinetic energy), considering the low Reynolds numbers studied in children. Thus, it appears that in children the laryngeal jet may produce turbulent airflow and result in greater particle deposition in the TB region. Further improvements in modelling of particle deposition in the TB region were proposed by Oldham and Robinson (2006) and took into account TB airway growth. Generally, computer dosimetric models use symmetrical infant, child, or adolescent TB geometries for dosimetric predictions; however, this idealized approach assumes an identical growth rate for all airways in the same generation (symmetrical growth), which is unlikely. To address this issue, Oldham and Robinson (2006) proposed the use of asymmetrical TB growth geometries (asymmetrical growth). The findings of this study indicated an improvement in the prediction for the inhaled monodispersed particle (0.1–20 μm diameter) deposition for steady inspiratory flow when using asymmetrical growth geometries rather than symmetrical growth geometry. Use of asymmetrical growth geometry may provide improved

estimates of regional particle deposition in infants, children, and adolescents. This work was, however, limited by the availability of complete airway morphometric information from only the first four TB generations obtained from 21 lung cast models (see Section 14.2.6.1).

14.2.4.2.4 Respiratory tract disease

As indicated in the US EPA 2004 AQCD, the presence of lung disease can significantly alter the dose of inhaled particles when contrasted with normally functioning lungs. For example, those with diseased lungs often experience increased particle deposition efficiency, less even distribution of inhaled air, altered airway particle deposition patterns and decreased particle clearance rates. Recent studies have shown that differences in particle deposition between diseased and healthy lungs mainly result from changes in lung morphology with progressing development of the insufficiency, and continuous adaptations of lung volumes (functional residual capacity (FRC), tidal volume (V_t)) and breathing patterns to the modified lung architecture) (Sturm and Hofmann, 2004, Bennett and Zeman, 2004; Chalupa et al., 2004; Phalen and Oldham, 2006).

Altered particle deposition efficiency has been observed for several prominent lung diseases, including COPD, emphysema and asthma. These changes are closely related to alterations in the distribution of inhaled air (and in the case of emphysema, exhalation of particles) common to each disease, and are explained by disease pathophysiology.

Compared with healthy subjects, patients with COPD show greater particle deposition in the TB region (US EPA, 2004). The increase in TB deposition corresponds to reductions in alveolar deposition; both are explained by the increased bronchoconstriction in the airway. Subjects with COPD generally tend to breathe at a faster rate, resulting in higher-than-normal tidal peak flow and resting minute ventilation and, consequently, greater particle deposition. Increased bronchoconstriction in combination with the altered breathing rates observed for COPD patients will, under standard breathing conditions, increase turbulent flow in the airway. Increased turbulence is generally correlated to higher levels of particle impaction in the upper airways. Mathematical models have corroborated experimental studies and in some cases specify airway obstruction as a major factor in increased PM deposition in the TB region in those with COPD. In one model of particle deposition in COPD subjects, Phalen and Oldham (2006) used a resting TB deposition enhancement factor of two to represent the anatomical effects in COPD patients. They also assumed that humans with COPD only ventilate 50% of their lungs. This implies that the surface doses in the ventilated portions of the lungs would be increased by an additional factor of two. These factors combined produce a 4-fold increase in the TB surface dose deposition over that of healthy adults.

An earlier study by Sturm and Hofmann (2004) modelled the influence of COPD and emphysema (or both) on the deposition of inhaled particles. In COPD patients, deposition of micrometer-sized particles increased with rising flow velocity and decreasing airway calibres, while bronchial deposition of UFPs was noticeably reduced. By contrast, emphysema was demonstrated to indirectly affect TB particle deposition due to changes in breathing behaviour; nonetheless, this disease influences particle behaviour in the alveoli to an appreciable extent. For any particle size, emphysematous lungs exhibit significant decreases in total alveolar deposition relative to normal lungs. This can be attributed to decreased airflow to the alveolar region that is the result of decreased alveolar elasticity, which is characteristic of emphysemic lungs, and restricts the lungs' ability to exhale gases from the deep lung. Since less air is being expelled, less air can be inhaled into the alveoli, resulting in decreased total alveolar deposition. Diseased lungs also exhibited a strong reduction in alveolar deposition per acinar airway generation compared with normal lungs—a factor directly related to the abnormal alveolar enlargement characteristic of emphysemic destruction of the alveolar walls. One factor that

should be considered for emphysemic patients is that due to the decrease in lung elasticity, a longer duration of potential exposure to inhaled particles may be occurring. This type of change may result in increased alveolar deposition of chemicals despite the decreased dose reaching the alveolar spaces.

Studies reviewed by the US EPA 2004 PM AQCD suggested that relative to healthy subjects, patients with moderate to severe airway obstruction received an increased dose from UFP exposure. This is likely due to the changes to lung morphology experienced by asthmatics, which will result in increased peripheral airway resistance (Martonen et al., 2003b). Changes such as bronchoconstriction, airway inflammation and thickening of the mucous layer will result in luminal constriction, especially in the peripheral areas of the lung, though abnormalities have been reported in the distal lung (Martonen et al., 2003b). Luminal constriction may increase the likelihood of particle impaction, leading to increased doses following particle exposure when compared against non-asthmatics. A study by Martonen et al. (2003b), using *in silico* models validated against human subjects, indicated that those with moderate to severe asthma had higher deposition of fine mode aerosols in the central airways compared with controls. Additionally, they found that in asthmatic subjects coarse mode aerosols had significantly reduced concentrations reaching the peripheral airways as a consequence of increased deposition in the central airways. Chalupa et al. (2004) reported similar results in 16 subjects with mild to moderate asthma symptoms exposed by mouthpiece to ultrafine carbon particles (count median diameter (CMD) 23 nm). Particle deposition was measured under spontaneous breathing at rest (minute ventilation, 13.3 ± 2.0 L/min) and under mild exercise (minute ventilation, 41.9 ± 9.0 L/min) conditions. The findings of this study indicated a significantly ($p < 0.001$) higher UFP deposition fraction in asthmatic subjects at rest as compared with healthy subjects (0.76 ± 0.05 vs. 0.65 ± 0.10 , respectively). Furthermore, in agreement with results reported by Daigle et al. (2003), the number deposition fraction increased as particle size decreased. The use of a mouthpiece for inhalation in this study might represent a bias in the results, inducing a greater difference in fractional deposition between healthy subjects and subjects with mild asthma. Breathing through a mouthpiece could promote a greater increase of V_t and minute ventilation in patients with asthma as compared with healthy subjects.

Other diseases that may result in changes to lung dosimetry, but which are not discussed in this document, include cystic fibrosis, tuberculosis, pulmonary fibrosis, acute or chronic pulmonary infections, and lung cancer.

14.2.4.2.5 Anatomical differences in humans

Similarly to differences in airway structure patterns between genders and between healthy and diseased subjects, interindividual anatomical variations in healthy subjects may affect particle lung deposition patterns and exposure doses. The US EPA 2004 PM AQCD reviewed a small number of studies investigating interindividual variation in lung deposition pattern for healthy subjects. These findings suggest that much of the variability in measured particle deposition among people occurred as a consequence of the differences in the size and shape of specific airway regions (i.e. differences in morphometry), including the nasal passages and TB conducting airways. Under controlled breathing conditions, measured intersubject variability in total and regional particle deposition could mainly be attributed to structural and volumetric differences in lung morphologies among different individuals, as suggested by theoretical predictions (Hofmann and Ashgarian, 2003).

14.2.5 Particle Clearance and Particle Overload

14.2.5.1 Mechanisms and Pathways of Clearance

Extrathoracic region (nasal epithelia): Particles deposited within the nasal passages (ET region) are cleared differentially, depending on the region of deposition and the chemical characteristics of the particle (US EPA, 2004). Especially for insoluble particles, posterior deposition is cleared by mucociliary transport towards the nasopharynx (with subsequent ingestion), while anterior deposition and subsequent mucociliary transport lead towards the vestibular region of the nasal passages, where clearance occurs by sneezing, wiping, or blowing. Soluble material/particles deposited on the nasal epithelium diffuse through the mucus and reach underlying cells. Once dissolved, substances can be translocated to the bloodstream of the nasal passages, which are well vascularised. Newman et al. (2004) in a study using nasally administered desmopressin demonstrated that plasma levels of the drug were affected by the site of deposition, with higher plasma concentrations being attributed to anterior deposition as a result of slower mucociliary clearance than observed at the posterior site. Translocation of UFPs across the olfactory epithelium and up the olfactory neuron, with subsequent accumulation in the olfactory bulb (Oberdörster et al., 2004; Elder et al., 2006) and brain (Oberdörster et al., 2004; Kim JS et al., 2006) has also been reported.

Tracheobronchial region: Poorly soluble particles deposited within the TB region undergo clearance through mucociliary transport towards the oropharynx, followed by ingestion. Depending upon the dose of exposure, the rate of mucociliary clearance, and proximity to specific cell types, particles may also cross the epithelium by endocytosis, entering the peribronchial region, where particles can be phagocytosed by airway macrophages. Poorly soluble particles may also enter the airway lumen from the bronchial or bronchiolar mucosa. Soluble particles may cross the epithelium and enter the systemic circulation, and there is evidence that they may also be cleared by mucociliary transport (US EPA, 2004).

Alveolar region: The US EPA 2004 PM AQCD provides a good analysis of the processes governing particle clearance in the alveolar space. Alveolar macrophages (AMs) participate in the non-absorptive clearance of poorly soluble particles deposited in the alveolar region through phagocytosis. Once phagocytosed, particles are typically cleared from the alveolar region either by transport toward the pharynx via a) the mucociliary system, b) transfer within the interstitium to a lymphatic channel, or c) possibly by traversing toward the alveolar–capillary endothelium and directly entering the bloodstream. The migration and grouping of particles and AMs within the lungs may lead to the redistribution of initially diffuse deposits into focal aggregates. Some particles or components of particles can also bind to epithelial cell membranes, to macromolecules, or to other cell components, delaying their clearance from the lungs. For soluble particles, absorptive processes involve dissolution into alveolar surface fluid followed by transport through the epithelium and into the interstitium, and then diffusion into the lymphatic or systemic circulation.

Recent research has focussed upon the specific clearance mechanisms for UFPs within the lungs. Since UFPs are so small (typically, in the nanometre scale) the mechanics of clearance may be distinct from larger particles, as direct, non-phagocytotic, rapid translocation via diffusion-like mechanisms has been described for UFPs in the lung (Takenaka et al., 2004, 2006; Geiser et al., 2005). Consequently, it is plausible that inhaled UFPs are translocated from the lung to the systemic circulation for clearance through other mechanisms, such as renal and hepatic excretion. These results may not hold true for all UFPs, as some research has not been able to demonstrate translocation of UFPs in humans (Wiebert et al., 2006a, 2006b), and results with UFPs should consider particle size, chemical composition, interaction with the cellular environment, solubility and other factors.

14.2.5.2 Clearance Kinetics

The actual time frame over which clearance of deposited particles occurs affects the cumulative dose retained by the respiratory tract, as well as the dose delivered to extrapulmonary organs (US EPA, 2004).

Extrathoracic region (nasal epithelia): In the nose, transport of poorly soluble particles deposited by mucus movement from the posterior to the anterior nasal passages occurs in approximately 10–20 min (US EPA, 2004).

Tracheobronchial region: Clearance of deposited particles from the TB region generally occurs in 24 h; however, there is some evidence that TB regional clearance has both a slow and a fast component. Experimental data have demonstrated that under some circumstances, 50% of deposited particles in the TB region cleared within 24 h of the onset of exposure, while the other half exhibited a biphasic clearance, with a small fraction of the deposited particles cleared with a half-life of 2–3 d and the rest with a half-life of 50–190 d (Möller et al., 2004).

Several factors are believed to influence TB particle clearance and may result in longer retention of deposited particles in the TB region under some circumstances. The TB region exhibits a rapid mucus movement; however, the speed of mucociliary clearance progressively slows in more distal airways. Specifically, there appears to be a slower clearance phase for particles deposited in the smaller bronchial tree (associated with bronchioles of a diameter <1 mm), suggesting that mucociliary transport may play only a minor role in the clearance of deposited particles from the smaller TB tree region. This was illustrated by Kreyling et al. (2004), who found that only 20% of deposited UFPs clear from the bronchiolar region by mucociliary clearance; the remaining fraction is retained long-term. Consequently, both greater deposition and less effective mucus clearance within this area could explain the enhanced particle burden at specific airway locations such as the one observed at airway bifurcations (US EPA, 2004). Additionally, the data from Möller et al. (2004) suggested that part of the long-term clearance mechanism could be driven by AMs.

Alveolar region: In comparison with airways where mucus transport is important, deposited particles in the alveolar region are cleared at a much slower rate, which is generally considered to be multiphasic (US EPA, 2004). Depending upon particle size and chemical composition, deposited particles in the alveolar region get phagocytosed rapidly (generally within 24 h of deposition) by AMs. The clearance speed of particle-loaded AMs via the mucociliary system depends on the site of uptake relative to the distal terminus of the mucus blanket. Some evidence has shown that clearance pathways and kinetics within the alveolar region depend on particle size. For instance, most fine particles larger than 100 nm are phagocytized by AMs; however, since UFPs may only partly be phagocytosed by AMs, it is expected that their clearance from the peripheral lungs may be different from that of larger particles (Kreyling et al., 2004; Semmler et al., 2004). It is generally assumed that clearance of UFPs occurs less through AMs than larger particles because of poor efficiency in phagocytosing UFPs, though some studies have reported no difference between pulmonary clearance kinetics of UFPs and larger particles (Semmler et al., 2004). Additionally, chemical activity at the particle surface, obstruction of cellular processes by physical presence of the particle at the macrophage surface, or both, could alter AM function. Moss and Wong (2006) proposed a dose–response metric based on the cumulative projected surface area of the particles vs. the cumulative surface of the exposed AM to describe the toxic effect (impairment of macrophage functions) caused by exposure to particles. Some studies have demonstrated the poor efficacy of AMs in recognizing and phagocytosing very small particles (Takenaka et al., 2004, 2006; Geiser et al., 2005). The scientific literature reports at least two different clearance processes for UFPs. In addition to phagocytosis by macrophages, mostly used for deposited particles larger than 0.1

µm, smaller UFPs seem to penetrate the boundary membranes of the lungs rapidly—a unique feature for insoluble particles. Whereas metallic silver and EC cleared effectively from the lung, iridium (Ir) and low concentrations of cadmium oxide (CdO) remained in the lung (Semmler et al., 2004; Takenaka et al., 2004, 2006; Geiser et al., 2005). Several particle properties could explain this discrepancy, including physicochemical properties of particles such as size, solubility *in vivo*, or binding affinity to the cell membrane. In addition to the solubility of particles, binding affinity of particles to the epithelial membrane could play a role in lung particle retention: for instance, with insoluble CdO UFPs, where Cd *in vivo* solubility did not seem to be a factor since Cd UFPs got retained in the lung (Takenaka et al., 2004). After a short-term exposure to CdO particles at low concentrations, deposited Cd particles may bind effectively to the cell membrane and be retained in the lung. However, at high Cd concentrations, systemic translocation took place, probably due to prior Cd destruction of the air–blood barrier (Takenaka et al., 2004).

Insoluble particles that are deposited within the alveolar region and not phagocytosed by AMs may cross epithelia within a few hours, entering the systemic or lymphatic circulation. Several investigations on inhaled particle dosimetry tried to confirm the occurrence of a translocation mechanism as part of the clearance process, and the US EPA 2004 PM AQCD reviewed a number of these studies. Small UFPs show greater access to the interstitium and lymphatic uptake than larger particles of the same material composition (US EPA, 2004). While inhaled, specific sizes of nanoparticles efficiently deposit by diffusional mechanisms in all regions of the respiratory tract. The smaller size of the particles facilitates their uptake into the cells and transcytosis across epithelial and endothelial cells into the blood and lymph circulation (Kreyling et al., 2004), and allows them to reach potentially sensitive extrapulmonary organs and to be excreted by renal or hepatic mechanisms (Semmler et al., 2004; Mills et al., 2006). While particle-specific properties, including the tendency of some forms to agglomerate, attenuated the movement into the circulatory system, evidence indicated the potential for translocation in time frames much less than 1 h. Subsequent accumulation in other organs (e.g. the liver) was found, though studies differed markedly in the proportion of UFP translocated.

Soluble particles clear rapidly from the alveoli by absorption through the epithelial surface and enter the systemic circulation. The absorption rate appears particle-size-dependent, with larger molecular weight solutes being cleared more slowly. The physicochemical properties of deposited particles may also influence the absorption rate. Similarly to absorbed insoluble particles, once in the circulatory system, dissolved particles may reach extrapulmonary organs; several studies demonstrating this phenomenon were reviewed by the US EPA (2004).

14.2.5.3 Particle Overload

Overload has been loosely defined as the alveolar burden causing a 2- to 4-fold reduction in alveolar clearance rates relative to normal clearance rates. The US EPA 2004 PM AQCD noted that the relevance of overload to humans is unclear, but that it may be an important factor for individuals with compromised lungs. In such lungs, the overwhelming of lung clearance mechanisms by particle overload could be relevant and could result in additional damage to already compromised tissues.

The phenomenon of particle overload in the rat lung following exposure to low-toxicity particles is of importance in the extrapolation of experimental animal data to humans in risk assessment. Impairment of particle clearance, interstitialization and lymph-node transfer of particles, chronic inflammation with epithelial cell proliferation, and eventually the development of lung tumours are known to occur in the rat at high lung burden, but this phenomenon is not observed in other rodents and it is not known whether it occurs in humans. Under conditions of overload, rats may

be more susceptible than humans, having decreased rates of alveolar clearance and of antioxidant defences (Brown et al., 2005).

14.2.6 Modelling Deposition in the Respiratory Tract

A variety of mathematical models have been developed in an attempt to provide insight into the mechanisms of deposition, clearance and retention within the lung. The advantage of these is in the ability to examine a wide variety of factors that are difficult or impossible to examine in live subjects. The US EPA 2004 PM AQCD provided an extensive review of such models. They characterized three elements necessary for the specification of a model: a mathematical description of the airway structure, a description of efficiency for various deposition mechanisms and anatomical structures, and a computational description of transport and deposition within the airways. Most models provide results consistent with experimental data in relation to a variety of issues, including the differential deposition of coarse and fine PM, greater deposition in children vs. adults, the influence of airway disease on deposition rates, and aggregation of very small particles within the airways with resultant impacts on deposition patterns. While additional verification and development of such models is necessary, it appears that they can be useful in understanding the deposition of PM within the respiratory tract and can contribute to the understanding of toxicological study results.

Airflow transport represents the primary mechanism for delivering airborne materials to various sites in the lung. Particle deposition in the human respiratory system is an extremely complex phenomenon, governed by a wide variety of overlapping and interacting factors (see sections 14.2.2, 14.2.3, and 14.2.4). Although in this context the term dosimetry modelling generally refers to mathematical models, some aspects of modelling also involve the use of cast models of the human or laboratory animal respiratory tract.

14.2.6.1 Cast Models

Cast models can be built using information obtained from magnetic resonance images or cadaver specimens. There are several advantages for the use of nasal moulds over that of live animals. First, deposition can be reproducibly measured over a wide range of air flows and particle sizes using one nasal mould. Second, the use of nasal moulds facilitates the measurement of particle deposition during the inspiration or expiration phases of breathing. Third, the use of nasal moulds makes it possible to measure particle deposition at a specific site in the airways by deconstructing the mould (Kelly and Asgharian, 2003). However, there are important differences in the airway geometry between nasal moulds made from a post-mortem case and the nasal airway of live animals. These include differences in elasticity of the airway passages, adherence of particles to the airway surface, air temperature and humidity in the airway passages, and the connecting device: tubing for the nasal mould or use of a mask for live animals.

In spite of these differences, the results of some studies indicate that good estimates of nasal deposition can be obtained by using rat nasal moulds as surrogates for their live counterparts in studies of the deposition of particles. For instance, deposition efficiency for PM sizes ranging from 0.5 to 4 μm measured in a rat cast model agreed well with results obtained from live animal studies (Kelly and Asgharian, 2003). Small differences in the construction of nasal airway cast models had minimal effects on nasal deposition efficiency for UFPs between 0.005 and 0.15 μm in size (Kelly et al., 2004a). In general, the trend of increasing deposition with decreasing particle size observed in this study agrees with previous studies of nanoparticle deposition in nasal replicas manufactured by different methods and based on different nasal airway data. In contrast, small differences in manufacturing of nasal airway replicates were significantly

associated with differences in inertial nasal deposition for particles larger than 1 μm (Kelly et al., 2004b). The authors attributed the difference in deposition efficiency in part to discrepancies in the use of assembly plates, and also in the surface roughness of the cast model. Generally, findings obtained with cast models concur with results acquired in experimental animal studies.

14.2.6.2 Computer/Dosimetry Models

Lung dosimetry models provide a biologically based, mechanistic approach to predicting the fate of inhaled particles, by describing the physical and physiological factors that influence the deposition, clearance, and retention of inhaled particles (Kuempel et al., 2006). The selection of a lung model is critical to accurately predicting the fate of inhaled particles. Generally, the vast majority of mathematical aerosol deposition models can be categorized as empirical, deterministic, or stochastic in nature (Martonen et al., 2005). While empirical models are based on fitting numerical relationships to experimental data, such as regional or total aerosol deposition, deterministic modelling quantifies both the physical nature of the lung and the fluid and particle dynamics associated with respiration by simplified mathematical expressions, and the resulting particle motion is calculated. Since deterministic models determine the simulated particle deposition patterns solely by the input parameters to the model, for any set of model input parameters, the same deposition pattern is found. In contrast, in stochastic deposition modelling, the input parameters do not receive discrete values, but rather use a distribution of values, which can in turn be based on experimental measurements. These morphometric parameters may include airway diameters, lengths, and branching angles. Reflecting the variation in the inputs, stochastic models generate outputs consisting of distributions of predicted output values, rather than point estimates alone.

14.2.6.2.1 Empirical models

The US EPA 2004 PM AQCD reviewed several mathematical models, including recent fluid dynamic models for particle deposition and two widely used mathematical models: the ICRP lung dose evaluation program (LUDEP) (ICRP, 1994) and the MPPD-1 model of the National Institute for Public Health and the Environment in collaboration with the CIIT Centers for Health (CIIT, 2005; Brown et al., 2005). Both models may be used to predict regional particle deposition in normal humans although, as expected, each computational model yields somewhat different deposition efficiencies. These computational models provide “averaged” deposition doses for the whole lung, TB region or other anatomical regions such as specific lung lobes and in some cases each TB generation. However, local deposition “hot spots” (areas of high deposition in comparison with surrounding surfaces) are not modelled. These mathematical models assume that all cells in a given airway receive the same particle deposition dose, and thus underestimate the local doses delivered to cells located in specific areas, such as carinas (e.g. flow dividers or bifurcation regions) in the TB region (Phalen and Oldham, 2006). In addition, they are limited in the particle sizes that are modelled; for example, the MPPD model only predicts particle deposition in the 0.01–20 μm particle diameter size range (Brown et al., 2005).

The US EPA 2004 PM AQCD noted that over the years, significant improvements have occurred in mathematical and computational fluid dynamic modelling of particle deposition, clearance and/or retention. Nevertheless, models using simplistic lung morphology and idealistic airflow patterns inevitably make a number of assumptions in deposition processes, and model predictions can vary substantially. Additional information on data input and limitations for the MPPD models can be found in the analyses by the US EPA (2004) and Brown et al. (2005).

14.2.6.2.2 Deterministic models

More recently, the increasing power of computer resources has led to the development of computational fluid particle dynamic (CFPD) models of the motion of particles as determined by CFD simulations. CFD modelling offers the flexibility of easily modifying such system parameters as flow rates, particle sizes, system geometry, and heterogeneous outlet conditions (Longest and Oldham, 2006). Typically, previous CFD models relied on cast measurements and idealized geometries, or the Weibel model of the lung, which is a series of recursive, symmetric bifurcations to simulate airflows and particle deposition patterns in pulmonary airways. Improvements in local aerosol deposition modelling with the use of CFD techniques provide an unprecedented approach for investigating inhaled particle deposition in realistic human airway geometries. The use of CFD techniques to predict local deposition patterns in the human respiratory tract requires the inclusion of detailed anatomical features of the airway structure, physiological parameters such as airway compliance, and relevant particle deposition mechanisms (inertial impaction, gravitational sedimentation, Brownian motion, thermophoretic, electrostatic, etc.).

The study of particle deposition by CFPD couples the mathematical solution of fluid velocities with the solution of particle trajectory equations developed from Newton's Second Law. The CFPD method takes into account the effects of complex flow patterns on particle motion and deposition in the respiratory system (Heraty and Quinlan, 2004; Martonen et al., 2005). In fact, the CFPD model generated by Martonen et al. (2005) suggested the presence of a transition from laminar flow to turbulent flow within the nasal passages during inspiration. To explain this, the authors proposed the presence of various flow structures, including bifurcating flows (at the edges of the turbinates), secondary flows (at curved airway passages), developing flows (at airway entrances and after bifurcations), and fully developed flows (within airways of sufficient length). Even within the same cross-section, flow structure may vary. For example, creeping (laminar) flow may exist between the turbinates, whereas highly convective (turbulent) flow may exist in the main passageway. This new approach agreed well with experimental data obtained from a human nasal cast model over a wide range of flow rates (4–30 L/min) and particle sizes (0.001–0.1 μm).

Asgharian and Price (2004) compared three human adult lung models of air flow transport. Results indicated that although the assumption of uniform air expansion and contraction of the compliant lung models appeared adequate for the predictions of regional and total particle deposition in the lung, the accurate prediction of local and site-specific deposition of particles may require more detailed lung ventilation models that take into account non-uniform lobar expansion caused by the pressure variation in the pleural cavity. Partridge and Javeed (2004) reported a computer model calculating the regional deposition of PM from a given volume of air as it enters the human body and travels through the respiratory tract. They found that several factors, including particle aerodynamic diameter, were identified as important particle characteristics in the prediction of ambient aerosol deposition. The findings of this study demonstrated that, although the particles with smaller aerodynamic diameter penetrated deep inside the respiratory tract (alveolar interstitial region), a significant amount of the smaller-size UFPs deposited in the ET region. In contrast, the vast majority of the coarse particles deposited in the upper region of the respiratory tract, although a small portion reached the deeper region of the lung. This report also considered new factors such as particle-adsorbed chemical partitioning characteristics and particle dissolution as factors influencing dose exposure during the transfer of particles along the respiratory tract and during deposition and clearance processes.

Oldham (2006) recommended several steps to improve CFD dosimetry modelling: first, improve the geometrical models used both in aerosol deposition experiments and in CFD simulations;

second, include all the significant particle deposition mechanisms in CFD simulations; third, achieve an agreement on the level of accuracy for validation of CFD predictions. Minard et al. (2006) proposed the use of a magnetic resonance imaging technique, which allows not only for gas visualization at fine anatomical scales but also for measurement of gas transport. Oldham also recommended that CFD models and experimental aerosol deposition studies need to include factors such as the motion of airways within living subjects due to both breathing manoeuvres and cardiac pulsations, as well as the thermal effects of inhaled aerosols and the airway surfaces.

Overall, the modelling of particle dosimetry provides a means of predicting total, regional, and local respiratory system concentrations of inhaled particles. In the future, the development and validation of increasingly sophisticated computational models that address particle deposition at local and regional scales, and ones that consider both biological variability and realism, will be instrumental in improving the prediction of the health effects of inhaled particles, especially in extrapolating the results of toxicological animal studies to humans (Martonen et al., 2005).

14.2.7 Interspecies Variation

Many data on PM toxicity originate from laboratory experiments in animals exposed either through inhalation or intratracheal instillation. Extrapolating findings from laboratory animals to humans exposed under similar scenarios requires a good understanding of the similarities and differences in PM dosimetry across diverse species. Comparing the results of dosimetry studies in animals to those in humans necessitates that the following be considered: 1) differences in laboratory exposure protocols and dosimetry calculation, 2) anatomical and physiological differences between human and animal lungs, and 3) incorporation of the above in interspecies model extrapolation.

14.2.7.1 Differences in Laboratory Exposure Protocol

Human particle inhalation protocols generally involve standardized breathing patterns. In contrast, laboratory animal studies can be conducted under diverse breathing conditions using spontaneous breathing, controlled ventilated breathing, and varying degrees of sedation. Moreover, the use of different exposure techniques such as nasal mask, oral mask, oral tube or tracheal intubation in animal models generates variability in regional deposition patterns.

Variation in particle size also affects the respiratory tract deposition pattern in humans and rats; also, relevance of the experimental particle size to ambient concentrations must be considered. The diverse particle size to which humans are routinely exposed complicates the extrapolation of rat dosimetric data, since laboratory experiments rarely expose animals to all particle-size modes (coarse, accumulation and ultrafine) simultaneously. Particle size, and consequently, particle size distribution are important because the deposition fraction and the region of deposition in the lung vary with particle size. The dosimetric implications of interspecies differences in deposition and clearance in rats and humans are discussed in Section 14.2.7.3.

Exposure duration represents yet another difference between rats and humans that requires consideration. The inhalation protocol in rats usually includes a daily 6-h exposure period to the tested air mixture followed by an 18-h exposure period to filtered air 5 d a week. In contrast, human exposure to PM occurs during the day while working, exercising or resting and continues at night while sleeping.

14.2.7.2 Anatomical and Physiological Differences between Human and Animal Lungs (with specific reference to rat anatomy)

The extrapolation of rat data to humans requires the characterization of species differences and of several caveats demonstrated in various mathematical models. Some differences commonly accounted for in interspecies extrapolation are provided in Table 14.4, which explores anatomical and physiological divergences between humans and rats.

Table 14.4 Anatomical parameters, and clearance and ventilatory values for humans and rats used in the dosimetry model calculations

	Human	Rat
Alveoli	4.86E+08	1.97E+07
Macrophage/alveolus	12.3	1.5
Macrophage, volume-capacity	1.5	1
Trachea, mucus velocity	5.5	1.9
Breathing route	Oro-nasal breather	Obligate nose breather
Lung symmetry	Symmetrical dichotomy	Monopodial
Bronchioles	Yes	No
Retention half-time, tracheobronchial	4–10 h	1–2 h
Retention half-time, alveoli	Up to 2 y	60–80 d

Source: Brown et al., 2005

Of these differences, two are particularly important to this discussion: disparities in the respiratory systems of the two species, and differences in clearance kinetics. Anatomically, the monopodial branching structure of the rat lung differs from the symmetrically dichotomous nature of the human lung. The rat lung structure allows for more penetration of large-size particles in the alveolar region (Brown et al., 2005). Also, rats lack respiratory bronchioles, which represent a susceptible site of disease in humans. Moreover, rats (and other animal species) are obligate nose breathers, whereas humans are normally nose breathers at rest and gradually switch to mouth breathing with increasing oxygen demand, as when under light or moderate exercise.

Furthermore, the rat clearance rate from the TB and alveolar regions exceeds that of humans. The retention half-time in the TB region ranges from 1 to 2 h in rats and from 4 to 10 h in healthy humans (Hoffmann and Asgharian, 2003). Consequently, rats retain less total deposited particle dose in the TB and alveolar regions than humans (Brown et al., 2005). Slower clearance from the alveolar region than from the TB region leads to retention half-times of 60–80 d in the rats but up to 2 years in humans. Moreover, rats chronically exposed to insoluble PM will reach steady state (the point at which particle clearance is balanced by particle deposition and the mass of PM retained in the lung approaches a nearly constant value) in a few months for the alveolar region, whereas humans will not reach steady state before 10 years of exposure. This is attributable to the more rapid clearance rate in rats compared with that of humans. In addition, rats are subject to PM overload leading to the overwhelming of both clearance and antioxidant defence.

14.2.7.3 PM Dosimetry in Rats versus Humans

As a consequence of the differences in respiratory structure and physiology, in contrast to humans most laboratory animals exhibit a near 100% deposition efficiency of particles greater than 5 µm AED in the ET region. Particles of that size range deposit somewhat less in the TB region of laboratory animals than in humans. This occurs because of the greater particle deposition efficiency observed in the ET region of laboratory animals (due to longer nasal passages and obligate nose breathing). Moreover, laboratory animals exhibit a smaller peak deposition fraction of 1 µm AED size particles in the alveolar region than humans (US EPA, 2004).

The consequences of differences in deposition efficiency in laboratory animals are well illustrated using the example of the rat. Defining a normalized dose in rats may require considerable adjustment of the rat exposure concentration in order to provide a dose equivalent to that of the environmentally relevant exposure level of humans. Under repeated low to moderate PM exposure level, rats require much higher exposure concentrations to show lung burden similar to that of humans, since rats exhibit a greater ET deposition fraction and a faster PM lung clearance than humans. Similarly, to achieve comparable acute dose per surface area in rats, relative to humans exposed to PM under moderate to heavy exercise, rats would need a higher PM concentration than that administered to humans.

An example of comparative dosimetry for particle exposure is illustrated by Miller et al. (1995). Their findings show that, while deposition on a mass per unit alveolar surface area is not different between humans and rats, dose metrics based upon particle number per various anatomical parameters (ventilatory unit, alveolus, or AM) exhibit marked differences between rats and humans, particularly for particles 0.1–0.3 µm in size. Based on the calculations per ventilatory unit or per alveolus, humans receive much greater numbers of particles than do rats when exposed to the same concentration and size of particles. The trend of differences between humans and rats is even more pronounced for the individuals with compromised lungs (smokers, asthmatics and patients with COPD) compared with normal subjects. Therefore, rats exposed to 1000–1500 µg/m³ of particles may actually have received the levels of particles equivalent to 120–150 µg/m³ in humans.

14.2.7.4 Interspecies Model Extrapolation

Use of data from species other than humans will require adjustment to the models commonly used to assess human dosimetry. Although the MPPD model uses the same mathematical equations for rat and human PM dosimetry, several host factors might confound the extrapolation of experimental animal data to humans when considering subject responsiveness/susceptibility to PM exposure. These factors include health status (diabetes, COPD, CVD), age (pulmonary development, immune system maturation) and breathing pattern (at rest, during exercise or during strenuous work). This presents further difficulties for the extrapolation of experimental animal dosimetric data to the general human population.

14.2.8 Summary and Considerations: Dosimetry

Understanding the biological effects of inhaled PM requires knowledge of PM dosimetry, because the biological response is due to the dose of particles at the target site. Deposition, clearance and retention are the elements of dosimetry. Dosimetric information is critical for understanding PM toxicity, including extrapolating effects found in toxicological studies of laboratory animals to those observed in humans, and for relating effects in healthy individuals to

those in susceptible populations. Our understanding of particle dosimetry has increased since the 1999 PM SAD.

Particle deposition in the respiratory tract is largely based on particle size, though breathing patterns also play an important role. For dosimetric purposes the respiratory tract can be divided into three regions: ET, TB, and alveolar. With nasal breathing, most coarse PM deposits in the ET region, though a significant fraction passes the nose to deposit in the TB and alveolar regions. Accumulation mode particles (AMPs) between 0.1 and 1 μm deposit primarily in the alveolar region, though there is increasing ET deposition at the upper end of this size range. UFPs deposit primarily in the alveolar region, though deposition in the ET and TB regions becomes increasingly important for the smallest UFP. Nasal versus mouth breathing has little or no effect on deposition for UFPs and AMPs, but breathing through the mouth deposits a greater fraction of coarse PM in the TB and alveolar regions as a result of bypassing the nose.

Factors such as gender, age, activity level, respiratory disease or interindividual anatomical differences can affect particle deposition through their effect on lung capacity, airway size, or breathing rate. Women generally exhibit greater fractional deposition of PM in the shallower airways than do men, though men can have a greater absolute deposition due to greater ventilation during spontaneous breathing. In most studies of healthy individuals, children had greater fractional deposition of PM than adults, whereas there do not appear to be marked differences among other age groups. During exercise, total and local deposition of PM is increased several-fold due to higher minute ventilation and a greater prevalence of oral breathing. Studies of particle deposition in people with airway obstruction as a result of respiratory tract diseases indicate that total lung deposition is generally increased, and that deposition can be enhanced locally in areas of active ventilation (airflow distribution is uneven in obstructive diseases).

Once particles deposit on the surface of the airways, they are then cleared from the respiratory tract or translocated to other sites within the body by distinct regional processes. Insoluble particles are often cleared by mucociliary transport and/or phagocytosis by macrophages, whereas soluble particles are generally cleared by other means (e.g. via the bloodstream).

Computational respiratory tract dosimetry models provide a biologically based, mechanistic approach to predict the fate of inhaled particles in laboratory animals and humans, by incorporating the physical and physiological factors that influence the deposition, clearance and retention of inhaled particles. However, while these models have become increasingly sophisticated and biologically realistic, experimental validation of their model predictions is still necessary.

There are important interspecies differences in particle deposition and clearance that the computational models can account for: e.g. by predicting the exposures needed to produce comparable doses in humans and laboratory rodents. However, a purely dosimetric adjustment for extrapolation from experimental animals to humans may well not be sufficient, as it is based on the unproven assumption that the same dose in the respiratory tracts of both species will result in the same effect. This will probably not be the case, as even between rodent species responses vary considerably. For example, rats, mice and hamsters differ markedly in the extent to which they exhibit pulmonary inflammatory and fibrinogenic effects in response to inhalation of highly insoluble particles. Given these limitations, the animal toxicology studies are best interpreted in terms of how the findings of such studies might lead to an understanding of the mechanisms that underlie the effects reported in the human epidemiological studies.

14.3 Animal Toxicology

14.3.1 Introduction

Experimental animal research provides valuable information about the biological effects of PM and the underlying mechanisms of action. Toxicology studies enable the testing of different types of PM over wide concentration ranges and under controlled laboratory conditions to determine and characterize functional changes, tissue and cellular damage, and dose–effect relationships. A broad array of endpoints can be investigated, and effects can be observed over the entire lifespan. *In vitro* studies using cell lines from humans and animals, increasingly more common in the literature, are also valuable for providing insight into the possible modes of action of PM toxicity.

There is considerable uncertainty in extrapolating results from animal studies and applying them to humans for risk assessment purposes, due to differences in species sensitivity, dosimetry and other complexities. It is important to bear in mind the significant anatomical differences between experimental animals and humans at all levels of the airway. As stated in the 1999 PM SAD, quantitative extrapolation of results from animals to humans for purposes of risk assessment requires not only consideration of differences in anatomical, morphological and functional aspects of the respiratory tracts, but also detailed dosimetric adjustments to account for exposure–dose–response relationships obtained from animal studies. For example, humans appear to receive much greater numbers of particles than do rats when exposed to the same concentrations and size of particles. Given these limitations, and bearing in mind the many dissimilarities between experimental animals and humans in terms of physiology, genetics and other biological characteristics, animal toxicology studies should be interpreted primarily in terms of how they may lead to an understanding of the range of biological responses that particles can elicit and/or the mechanisms that may underlie effects reported in epidemiological and controlled human exposure studies. It should also be kept in mind that the use of very high exposure levels in some studies relative to ambient concentrations raises uncertainty as to their relevance to the risk assessment of health effects.

In this section, the results of recent animal and *in vitro* toxicology studies of the biological responses elicited by PM and the potential mechanisms of action involved are reviewed, and new findings are compared with those discussed in previous assessments (the 1999 PM SAD and the US EPA 2004 PM AQCD) to determine how the state of knowledge in this field has evolved. There continues to be a considerable amount of research on the effects of PM on a wide range of health endpoints, most of it focused on the pulmonary and cardiovascular systems. These systems are generally thought to be the most sensitive targets of PM toxicity, although there are now indications that other systems (e.g. the nervous system) may also be important targets. Recent years have seen a proliferation of studies seeking to replicate and test the complex ambient particle mix, either with resuspended ambient PM or through the use of particle concentrators that generate concentrated ambient particles (CAPs) from specific locales in real time. There has also been heightening interest in the UFP fraction, with the new term *nanotoxicology* referring to the study of the health effects of nanoscale material, which includes UFPs. An increasing amount of research has also aimed at characterizing the relationship between toxicity and PM constituents and sources, location, and season.

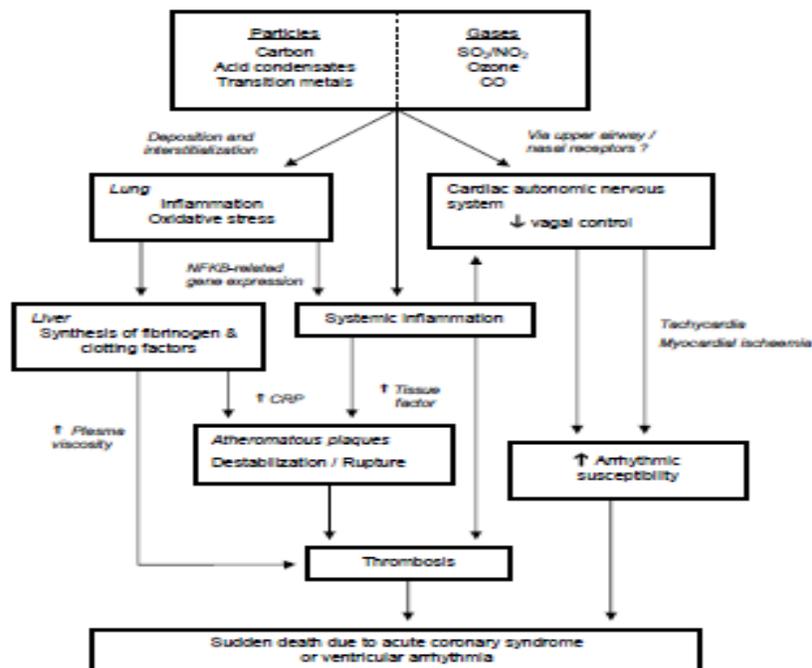
14.3.2 Cardiovascular Effects of PM

It was noted in the 1999 PM SAD that epidemiological studies conducted in Canada and the US had shown a consistent association between fine PM air pollution and increased hospital admissions due to CVD. However, up until that time only a handful of studies using

experimental animals had examined cardiovascular responses. Initial evidence for cardiovascular effects included electrocardiographic (ECG) abnormalities, such as dose-related increases in arrhythmias and skipped heartbeats, in rats and dogs following exposure to residual oil fly ash (ROFA). The mechanism for particle-induced cardiovascular responses was not clear at the time of the 1999 PM SAD.

By the time of the US EPA 2004 PM AQCD, growing epidemiological and toxicological evidence was beginning to show that the cardiovascular system was an important target of PM toxicity that may be related to certain health endpoints such as mortality. Toxicological evidence of cardiovascular responses to inhaled PM led to a number of hypotheses for explaining the effects, including cytokine effects on heart tissue, alterations in blood coagulability, perturbations in arrhythmogenic mechanisms, changes in endothelin levels, and involvement of neural reflexes. However, it was noted that the link between PM-induced changes in cytokine production in the lung and effects on cardiovascular function was not clear, strong conclusions could not be drawn about the relationship between PM exposure and blood coagulation, and there was no consistent evidence that ambient PM levels affected HRV, conduction system function, and hematopoiesis. Research on the adverse effects of PM on the cardiovascular system has continued to accelerate, and Table 14.5, Section 14.3.2 presents a qualitative summary of particle effects on the cardiovascular system in animal toxicology studies. Figure 14.12 shows the many potential pathophysiological mechanisms involved in these effects.

Figure 14.12 Potential pathophysiological mechanisms for the effects of air pollutants on the cardiovascular system (Source: adapted from Routledge and Ayres, 2005)



14.3.2.1 Cardiovascular Injury, Inflammation and Atherosclerosis

The US EPA 2004 PM AQCD stated that the link between PM-induced inflammation and effects on cardiovascular function was not clear. The results of some studies with compromised animal models supported this hypothesis, while other studies with normal dogs and rats failed to show changes in ECG consistent with those observed in compromised animals. It was stated that

more basic information on the effects of mild pulmonary injury on cardiovascular function was required to more fully evaluate this hypothesis. Additionally there was only very limited evidence for an effect of PM on the progression of atherosclerosis: one study had found that exposure of Watanabe heritable hyperlipidemic rabbits to PM₁₀ caused progression of atherosclerotic lesions toward a more advanced phenotype and increased the vulnerability to plaque rupture.

Recent studies provide some evidence for particle-induced tissue damage and inflammatory effects on the cardiovascular system. A retrospective analysis was made of studies involving inhalation exposure of mice to nine different particulate metal compounds (mass median aerodynamic diameter (MMAD) of ~1–2 µm) over a 2-year period. It found that high-dosed animals developed significantly increased incidences of coronary and renal arteritis (an influx of mixed inflammatory cells and partial or complete effacement of the normal vascular wall architecture) over controls in two of nine studies (0.3 mg/m³ indium phosphide and 3 mg/m³ cobalt sulphate heptahydrate), while marginal increases were detected in two other studies with vanadium pentoxide and gallium arsenide (Moyer et al., 2002). Arteritis of the muscular arteries of the lung was not observed. In phase two of the study, arteritis did not develop in mice exposed subchronically to higher levels of the compounds.

Kodavanti et al. (2003) found that chronic inhalation of 10 mg/m³ ROFA PM_{2.5} containing bioavailable Zn as the primary water-leachable metal caused histologically discernible myocardial injury, inflammation and degeneration in rats at a concentration that did not cause significant lung injury. Rivero et al. (2005b) reported that intratracheal instillation of rats with PM_{2.5} collected from São Paulo, Brazil, caused increased lymphocyte counts (at 100 µg PM_{2.5}), hematocrit and heart wet-to-dry weight ratio (at 500 µg), and total reticulocytes (immature red blood cells (RBCs)) at both doses. Segmented neutrophils and fibrinogen were decreased at 100 µg. Histological changes were associated with significant vasoconstriction in pulmonary arterioles.

The influence of particulate exposure on the progression of atherosclerosis has become a potentially important mechanism for explaining the cardiovascular effects of PM. Apolipoprotein E-deficient (ApoE^{-/-}) mice are a murine model of advanced aortic plaque used to study atherosclerosis. The use of these hypercholesteremic mice as a model for human atherosclerosis has been criticized because of their extremely high blood cholesterol levels and rapid development of cardiovascular lesions in comparison with humans; however, the overall pathologic process is similar. As part of a series of collaborative chronic inhalation studies by researchers at New York University, Chen and Nadziejko (2005) examined the effects of CAPs exposure on the exacerbation of atherosclerosis using ApoE^{-/-} mice as well as double knockout (DK) mice lacking apolipoprotein E and the low-density lipoprotein receptor (ApoE^{-/-} LDLr^{-/-}). Mice were exposed daily for 6 h, 5d/week for up to 5 months to an average PM_{2.5} concentration of 110 µg/m³. All DK mice, regardless of exposure, developed extensive lesions in the aortic sinus regions; lesion areas covered more than 79% of the total area. In male DK mice, CAPs appeared to enhance the lesion areas in the aortic sinus regions, with changes approaching statistical significance (p = 0.06). Plaque cellularity was also increased by 28% (p = 0.014, combined) while there were no CAPs-associated changes in the aortic lipid content of these mice. Both ApoE^{-/-} and DK mice had prominent areas of severe atherosclerosis covering 40% or more of the luminal surface of the aorta. CAPs exposure increased the percentage of aortic intimal surface covered by grossly discernible atherosclerotic lesions by 57% in ApoE^{-/-} mice (p = 0.03); changes produced in male (10% increase) or female (8% decrease) DK mice were not statistically significant. Air and CAPs-exposed normal healthy C57Bl/6 mice were devoid of vascular lesions, with the exception of a few small fatty streaks.

A related study by Sun et al. (2005) found evidence of PM-induced vascular inflammation and potentiation of atherosclerosis. ApoE^{-/-} mice were fed normal chow or high-fat chow and then

chronically exposed by inhalation to CAPs at a mean PM_{2.5} concentration of 85 µg/m³. Mice fed high-fat chow and exposed to PM_{2.5} showed significant increases in macrophage infiltration, increased generation of reactive oxygen species (ROS) in aortic sections, increased expression of inducible nitric oxide synthase (iNOS), and greater immunostaining for the protein nitration product 3-nitrotyrosine in plaque. The latter two endpoints were also increased by CAPs exposure in mice fed normal diets. The mean composite plaque area was higher overall in mice from the high-fat chow group, and exposure to PM_{2.5} increased plaque area in both groups, to a significant level in the high-fat chow group ($p < 0.001$). Lipid content in the aortic arch was increased 1.5-fold in mice fed high-fat chow and exposed to PM_{2.5} compared with filtered air exposure. A normal healthy mouse strain was not included in this study for comparison. *In vitro*, Vogel et al. (2005) reported that concomitant with the induction of inflammatory factors, the accumulation of total cholesterol was significantly increased in DEP- or urban dust-treated macrophages, a hallmark of foam cell formation that *in vivo* may contribute directly to the progression of atherosclerosis and other cardiovascular events.

14.3.2.2 Hemodynamic Effects and Blood Coagulability

The US EPA 2004 PM AQCD stated that the published toxicological evidence bearing on whether moderate lung inflammation increases blood coagulability was mixed and inconsistent, and it drew no conclusions about the relationship between PM and blood coagulation. In addition, consistent evidence that PM ambient concentrations could affect hematopoiesis remained to be demonstrated. It was also stated that more research was needed on the effects of PM on arterial blood gases and pulmonary function in order to fully address the hypothesis that the heart may be adversely affected by the impairment of oxygenation and increased work of breathing secondary to lung injury. At that time, studies appeared to indicate that ambient PM was unlikely to cause severe disturbances in oxygenation or pulmonary function.

No recent literature on the impairment of blood oxygenation by PM has been identified, but recent studies have looked at thrombogenic responses to particle exposure. Khandoga et al. (2004) reported that intra-arterial infusion of ultrafine CB induced platelet accumulation in the hepatic microvasculature of healthy mice that was associated with prothrombotic changes on the endothelial surface of hepatic microvessels. Silva et al. (2005) found a dose-dependent enhancement of peripheral thrombus formation following intravenous injection of rats with 60 nm ultrafine polystyrene particles. However, the relevance to pulmonary exposure of data from animals exposed via the intravenous route is uncertain. Intratracheally instilled positively charged 60 nm ultrafine polystyrene particles enhanced vascular thrombosis within 1 h after deposition in the respiratory tract of hamsters, but not dose-dependently, while similarly sized particles with neutral or negative charges and particles with similar surface charge but larger size (400 nm) did not have this effect (Nemmar et al., 2003). A further study with hamsters investigated experimental thrombosis in photochemically induced femoral vein lesions in association with lung cellular infiltration 24 h after instillation of silica particles with a median size of ~2 µm. Particles induced pulmonary inflammation with stimulation of peripheral platelet-rich thrombus formation, accompanied by increased neutrophil elastase levels in bronchoalveolar lavage (BAL) and plasma (Nemmar et al., 2005). These findings have implications for the worsening of cardiovascular injury/disease states, suggesting a role for macrophage–neutrophil cross-talk during lung inflammation that leads to release of neutrophil elastase into the systemic circulation, which may then prime platelet activation and contribute to the development of a thrombotic tendency when the primed platelets encounter an injured vessel wall.

Several recent studies have analyzed fibrinogen, a plasma protein involved in blood clotting. Kodavanti et al. (2005) describe multiple CAP inhalation studies conducted over 2 years with rats. Despite consistent and high CAP concentrations in the 1-d exposure studies, no cardiopulmonary effects were noted. Exposure concentrations varied among the seven 2-d

exposure studies, ranging from 144 $\mu\text{g}/\text{m}^3$ to 2758 $\mu\text{g}/\text{m}^3$, during which a consistent increase of plasma fibrinogen and lavage fluid gamma-glutamyltransferase activity was demonstrated in spontaneously hypertensive (SH) rats. The SH rat is an animal model commonly used for studying human hypertension and CVD. The effect on fibrinogen was less consistent in normotensive Wistar-Kyoto (WKY) rats but still statistically significant when all groups were combined. Decreased total cell counts and AMs and increased neutrophils were observed in WKY rats only. Water-soluble metals and organic enrichment of the particles appeared to be more critical in eliciting acute health effects than CAP mass concentrations, especially the association between increased plasma fibrinogen and Zn and OC. Cassee et al. (2005) reported that 1-d inhalation exposures of SH rats to CAPs from three sites in the Netherlands produced an overall effect of increased blood fibrinogen concentrations when using CAP exposure as a binary term. CAPs were 0.15–2.5 μm in size and their time-integrated mass concentrations ranged from 270 $\mu\text{g}/\text{m}^3$ (suburban) to 3720 $\mu\text{g}/\text{m}^3$ (industrial). Normal healthy rats were not used for comparison.

Two types of similarly sized fine particles from industrial combustion sources, PSA and PSB, were found to induce leucopenia, elevation of plasma fibrinogen levels, and bone marrow and pulmonary inflammatory changes to a greater extent than carbon particles or saline controls when intranasally instilled in mice at a dose range of 0.1–10 μg (Medeiros Jr. et al., 2004). ROFA from a solid waste incinerator rich in cerium (Ce), cobalt (Co), lanthanum (La) and V, designated PSA, induced a greater increase in the production of erythroblasts in bone marrow and histological pulmonary inflammation in both the interstitial and perivascular areas of the lung. Iron-rich particles retrieved from the electrostatic precipitator of a steel plant chimney, designated PSB, elicited pulmonary inflammation in the perivascular area only, but had a greater effect in increasing plasma fibrinogen levels. Gerlofs-Nijland et al. (2005) reported that plasma fibrinogen in SH rats was elevated at 24 and 48 h following intratracheal instillation of 10 mg/kg EHC-93 Ottawa urban particles or road tunnel dust from Hendrik-Ido-Ambacht, the Netherlands. Lower doses of road tunnel dust (0.3–3 mg/kg) did not have this effect, and neither particle produced significant changes in plasma levels of von Willebrand factor, a marker of endothelial injury, or big ET-1, the precursor of the vasoconstrictor endothelin-1 (ET-1). Kooter et al. (2005) isolated total lung RNA (ribonucleic acid) from SH rats 2–40 h after intratracheal instillation of EHC-93 at 10 mg/kg. In addition to genes involved in the oxidative stress response, upregulated genes included those involved in coagulability and cardiovascular function, such as fibrinogen, coagulation factor 3, inducible nitric oxide synthase and angiotensin-1-converting enzyme 1.

Two recent studies do not support the concept of a particle-induced and inflammation-mediated prothrombotic state. Harder et al. (2005) found no evidence of an inflammation-mediated increase in blood coagulability following 24-h exposure of WKY rats to 38 nm carbon UFPs at 180 $\mu\text{g}/\text{m}^3$. Inhalation did not induce any significant changes in plasma fibrinogen or factor VIIa levels, and there were no prothrombotic changes in the lung or heart at the protein or messenger ribonucleic acid (mRNA) level. Another study found altered fibrinogen levels in healthy Wistar rats intratracheally instilled with 100 μg of $\text{PM}_{2.5}$ collected in São Paulo, Brazil, but levels were reduced rather than increased (Rivero et al., 2005b).

In vitro studies have examined mechanisms potentially involved in the thrombogenic effects of particles. Culture media from macrophages and 16HBE bronchial epithelial cells, but not A549 cells, exposed to PM_{10} from urban sites in London, UK, had an enhanced ability to cause clotting in the pooled plasma recalcification time assay (Gilmour et al., 2005). Tissue factor gene expression was also enhanced in macrophages exposed to PM_{10} . Gursinsky et al. (2006) reported that exposure of primary cardiac ventricular fibroblasts to fly ash (<20 μm) promoted fibrosis by reducing matrix metalloproteinase (MMP) and inducing collagen expression, while

also enhancing the formation of disease-related advanced glycation endproduct modification of various cellular proteins. A study by Furuyama et al. (2006) found that exposure of endothelial cells to either diesel exhaust particles (DEPs) or the soluble organic fraction of urban PM from Urawa, Japan, induced oxidative stress and reduced the production of plasminogen activator inhibitor-1 (PAI-1). PAI-1 inhibits fibrinolysis, the physiological process that degrades blood clots. This finding suggests that the soluble fraction of these particles may promote fibrinolysis and reduce clotting, therefore not supporting a thrombogenic mechanism.

14.3.2.3 Effects on the Vasculature

The vasoactivity of PM remained a hypothesis with little supporting experimental animal data at the time of the US EPA 2004 PM AQCD, aside from the limited amount of evidence suggesting that high doses of inhaled ambient PM were capable of causing a vasopressor response and affecting blood levels of endothelin in rats without causing acute lung injury. Since then more research has focused on vasoactivity and the resulting changes in blood pressure as potentially important mechanisms for the cardiovascular toxicity of PM.

In recent studies, short-term exposure to PM has been observed to induce vasoconstriction. Exposure to CAPs (median 182.75 $\mu\text{g}/\text{m}^3$, range 73.5–733 $\mu\text{g}/\text{m}^3$) for 3 d at 5 h/d was shown to induce vasoconstriction of the small pulmonary arteries in normal rats compared with those exposed to filtered air, although no significant effect of particle exposure was found for rats with chronic bronchitis induced by pretreatment with SO_2 (Batalha et al., 2002). Lumen/wall area (L/W) ratios decreased, indicative of vasoconstriction or impaired vasodilation, as concentrations of fine particle mass, Si, Pb, sulphate, EC and OC increased when all animal data (normal and chronic bronchitis) were analyzed together. In separate univariate analysis, the association for sulphate was significant only in normal rats, whereas Si was significantly associated with reduced L/W ratios in both normal rats and rats with chronic bronchitis. In multivariate analyses including all particle factors, the association with Si remained significant.

Rivero et al. (2005b) reported an effect on pulmonary vasculature in healthy rats exposed to particles collected in São Paulo, Brazil. A significant dose-dependent reduction of the intra-acinar pulmonary arteriole L/W ratio was detected in rats at doses of 100 and 500 μg of tracheally intubated $\text{PM}_{2.5}$, while the L/W of peribronchiolar arterioles decreased at 500 μg . A study using microarrays demonstrated that along with increased expression of acute inflammatory mediators such as interleukin (IL)-1 and tumour necrosis factor (TNF), the expression of vasoconstriction mediators (e.g. endothelin, vascular cell adhesion molecule (vCAM)) was increased and the expression of endothelial nitric oxide synthase (eNOS), a vasodilation mediator, was decreased in rats exposed for 3 d to CAPs with a mean mass concentration of 262.21 $\mu\text{g}/\text{m}^3$ and a mean (\pm SD) particle size of $0.27 \pm 2.3 \mu\text{m}$ (Godleski et al., 2002).

Nurkiewicz et al. (2004) reported that intratracheal instillation of 0.1–2 mg ROFA in healthy rats dose-dependently impaired systemic endothelium-dependent arteriolar dilation in the spinotrapezius muscle compared with saline-treated rats. This effect occurred independently of detectable pulmonary inflammation, as rats exposed to less than 1 mg ROFA or TiO_2 did not exhibit signs of pulmonary damage or inflammation. Venular leukocyte adhesion and rolling was significantly increased in ROFA-exposed rats, suggesting local inflammation at the systemic microvascular level. The sensitivity of arteriolar smooth muscle to NO was similar in saline-treated and ROFA-exposed rats, suggesting that ROFA exposure affected endothelial rather than smooth muscle function and that exposure to ROFA or TiO_2 resulted in similar alterations of systemic microvascular function, arguing against soluble metals being a prime factor in this response. Subsequent work confirmed these findings and provided evidence that impairment of endothelium-dependent dilation in the systemic microcirculation coincided with

polymorphonuclear leukocyte (PMN) adhesion, myeloperoxidase deposition, and local oxidative stress, mechanisms that may contribute to the disruption of the control of peripheral resistance associated with PM (Nurkiewicz et al., 2006). Exposure to ROFA or TiO₂ did not affect microvascular constriction in response to the adrenergic agonist phenylephrine.

Dvonch et al. (2004) reported that plasma concentrations of asymmetric dimethylarginine, which is a circulating endogenous inhibitor of the vasodilation mediator nitric oxide synthase (NOS) associated with impaired vascular function, were significantly elevated in rats exposed for 3 d at 8 h/d to CAPs from Detroit, Michigan, with an average concentration of 354 µg/m³, as compared with animals exposed to filtered air. Analyses of meteorological data and CAP trace element composition (elevated S, V, La, Ce and samarium (Sm) with increased CAP mass) suggested that local particle emissions from a nearby industrial source complex contributed largely to the overall mass of CAPs measured over the exposure period.

In chronic studies of vascular responses to PM, Sun et al. (2005) reported that ApoE^{-/-} mice fed high-fat chow and exposed to CAPs at a mean PM_{2.5} concentration of 85 µg/m³ for 6 months displayed an alteration of vasomotor tone compared with mice exposed to filtered air. This change was indicated by heightened vasoconstrictor responses to phenylephrine and serotonin challenge in the thoracic aorta and attenuated relaxation to the endothelium-dependent agonist acetylcholine (ACh). Another study found a significant decrease of L/W ratio in pulmonary (p = 0.03) and coronary (p = 0.021) arteries of neonatal mice following 4 months of exposure to ambient levels of air pollution in downtown São Paulo, Brazil, while no significant changes were noted in control animals exposed to filtered air (Lemos et al., 2006). Renal vessels were not affected. The mean 24-h PM₁₀ concentration during the exposure period was 35.52 ± 12.84 µg/m³. In addition to PM₁₀ the ambient air contained gases such as NO₂ and CO, as well as other pollutants, and the control chamber was not completely devoid of PM and gaseous pollutants. Therefore the contribution of particles to the observed effects could not be determined.

In contrast to evidence for a vasoconstrictive effect of PM, Bagate et al. (2004b) reported that instillation of PM (EHC-93, 10 mg/kg) or lipopolysaccharide (LPS) in SH rats caused a significant increase in receptor-dependent vasorelaxation of aorta (compared with saline-instilled rats) that was maximal at 4 h. The effect at 24 h was much smaller, although this coincided with maximal pulmonary inflammation. Blood metal analysis showed an increase of Zn and V concentrations at 1 and 4 h postinstillation. *In vitro*, both ambient particles of EHC-93 and its water-soluble components failed to modify the resting tension of rat aorta and small mesenteric rat artery but caused a dose-dependent vasorelaxation in precontracted blood vessels (Bagate et al., 2004a). In a further study, EHC-93 and its soluble components (Cu²⁺- or Zn²⁺-containing solutions) elicited a dose-dependent and endothelium-independent vasodilation in rat aorta rings that was mainly linked to the activation of soluble guanylate cyclase in the vascular smooth muscle, since its inhibition by NS2028 almost abolished relaxation (Bagate et al., 2006a). Vasodilation responses were significantly higher in aorta rings of SH compared with WKY rats. Li et al. (2006) found contrasting *in vitro* results: they reported that urban standard reference material (SRM) 1648 particles induced vasoconstriction in pulmonary arterial rings with phosphorylation of ERK1/2 and p38 MAPKs (mitogen-activated protein kinases), and H₂O₂ (hydrogen peroxide) produced by NAD(P)H oxidase, but not a mitochondrial source, appeared to contribute to the PM-induced vasoconstriction.

Endothelins are peptides produced mainly in the endothelium that play an important role in vascular homeostasis due to their strong vasoconstricting activity. There is some evidence that these molecules may be involved in the cardiovascular responses elicited by PM. Serum total endothelin concentrations were significantly elevated in both rats with myocardial infarction (MI) and controls in response to intratracheal instillation of 2 mg PM_{2.5} from an industrial area (Kang

et al., 2002). However, increased numbers of the endothelin receptor type A on cardiomyocytes were only observed in the infarct myocardium. Elder et al. (2004b) reported that short-term exposure of rats to particle aerosol via an on-road exposure system in New York State significantly increased plasma endothelins. Particle mass concentration was estimated to be in the range of 37–106 $\mu\text{g}/\text{m}^3$, and the average daily geometric number mean particle size ranged from 15 to 20 nm. Thomson et al. (2005) exposed rats to particles (0–50 mg/m^3 EHC-93), ozone (0–0.8 ppm (parts per million)) or combinations of particles and ozone for 4 h and found that PM and ozone independently upregulated the expression of lung endothelin system genes. *In vitro*, Chauhan et al. (2005) reported complex changes in the expression of genes associated with the endothelin system following exposure of A549 cells to ambient particles. Results indicated that alveolar epithelial cells (AECs) may not be the source of elevated blood ET-1 seen *in vivo* after inhalation of urban PM. However, these cells can produce higher levels of endothelin-converting enzyme-1 and therefore may initiate paracrine and autocrine conversion of big ET-1 into mature peptide in macrophage and epithelial cells; in addition, they may produce high levels of cytokines (IL-8 and vascular endothelial growth factor) involved in endothelin synthesis.

The endothelium is the thin lining of endothelial cells forming the interior surface of blood vessels, and *in vitro* studies have examined the responses of these cells to PM. Yamawaki and Iwai (2006) reported that vascular endothelial cells treated for 24 h with CB having a mean diameter \pm SD of $0.248 \pm 0.161 \mu\text{m}$ displayed cytotoxic morphological changes and induction of proinflammatory molecules, while expression of connexin37 in gap junctions and eNOS was reduced. The results suggest that CB may directly affect the endothelium, causing cytotoxic injury, inflammatory responses and inhibition of cell growth. NO is anti-atherogenic and anti-thrombogenic; therefore particle-induced reduction of NO in the endothelium is a possible mechanism for air pollution-related atherosclerosis and ischemic heart disease (IHD). Li et al. (2006) reported that increased H_2O_2 production in endothelial cells in response to urban SRM 1648 particles came from two major sources, the NAD(P)H oxidase and the mitochondrial electron transport chain, since it was suppressed by inhibitors for these systems but not by inhibitors for other systems. The water-soluble fraction of these particles, as well as Cu and V, also stimulated H_2O_2 production.

14.3.2.4 Direct Effects on Cardiac Function

The US EPA 2004 PM AQCD noted that although changes in heart rate, HRV and conduction system function had been reported in some animal studies using high doses of inhaled or instilled particles, not all studies had shown consistent alterations. Several studies using normal dogs or rats failed to show changes in ECG consistent with what was observed in other studies using compromised animal models. Some evidence appeared to support the hypothesis that particles could potentially be transported to the heart to exert effects directly on cardiac vasculature or heart muscle itself. An alternative hypothesis was that particles may exert rapid effects on cardiac function through the stimulation of nerve ending receptors in lung tissue, resulting in the secretion of inflammatory messenger substances and/or the activation of neurally mediated autonomic reflexes. The causal relationships between PM-related systemic cardiovascular effects and potential life-threatening alterations in cardiac function were not fully established at that time.

Recent experimental animal studies have found evidence of particle-induced ECG waveform abnormalities and increased frequency of arrhythmia. Kang et al. (2002) reported that exposure of rats with induced MI to $\text{PM}_{2.5}$ from an industrial area of Louisville, KY, by intratracheal instillation (2 mg) significantly worsened their ventricular arrhythmia and further decreased their heart rate, while the same exposure in sham-operated control animals did not cause significant changes. Nadziejko et al. (2004) observed increased frequency of arrhythmias involving the sino-atrial node (such as skipped beats and pauses), symptomatic of atrial-ventricular

conduction blocks, in aged rats acutely exposed nose-only to $\sim 180 \mu\text{g}/\text{m}^3$ CAPs from Tuxedo, NY, for 4 h, while exposure to $\sim 890 \mu\text{g}/\text{m}^3$ ultrafine carbon or 1.2 ppm SO_2 did not produce an effect. Wichers et al. (2004a) reported dose-related rhythm disturbances, including lengthened R-R intervals, skipped beats and bundle branch blocks, in SH rats instilled with 3.33 and 8.33 mg/kg of PM from the inside wall of a power plant stack burning residual oil (RO). These disturbances appeared to subside within 48 h. Control animals and those dosed with 0.83 mg/kg PM had an infrequent incidence of arrhythmias. Wold et al. (2006) observed that intravenous infusion of ultrafine DEP caused ventricular premature beats (VPBs) in two of three rats, and ambient UFPs slightly increased ejection fraction ($\sim 4.5\%$), while this parameter was unchanged in rats receiving ultrafine DEP or saline. UFPs also caused blood pressure changes in isolated perfused rat hearts, while the soluble fraction containing no particles did not produce this effect. Campen et al. (2006) reported that in comparison with gasoline emissions free of particulates or with much higher levels of resuspended road dust, fresh particulates from gasoline engine exhaust ($60 \mu\text{g}/\text{m}^3$, 6 h/d for 3 d, average PN mean diameter of 15 nm) elicited increases in the deviation of T-wave area on the ECG of ApoE^{-/-} mice on a high-fat diet. T-wave changes indicate alterations in cardiac repolarization. Gasoline PM also increased plasma ET-1 levels but did not affect markers of systemic inflammation.

These studies support previous data such as those found in Wellenius et al. (2002), who reported that exposure of infarcted rats to ROFA, but not CB or room air, increased the frequency of arrhythmia and decreased HRV in animals with pre-existing premature ventricular complexes. By contrast, more recent studies by Wellenius and colleagues determined that, overall, exposure of myocardial-infarcted rats to CAPs from Boston, MA, for 1 h did not significantly affect the frequency of ventricular arrhythmias (median concentration $350.5 \mu\text{g}/\text{m}^3$; Wellenius et al., 2004) or supraventricular arrhythmias (mean concentration $645.7 \mu\text{g}/\text{m}^3$; Wellenius et al., 2006).

In studies with dogs, Wellenius et al. (2003) reported that inhalation of CAPs from Boston at a median concentration of $285.7 \mu\text{g}/\text{m}^3$ (range $161.3\text{--}957.3 \mu\text{g}/\text{m}^3$) exacerbated myocardial ischemias in mongrel dogs during coronary artery occlusion as revealed by significantly enhanced occlusion-induced peak ST-segment elevation. This effect was correlated with the Si concentration of the particles and other crustal elements possibly associated with urban street dust, but not with CAP mass or number concentrations (NCs). Conversely, Muggenburg et al. (2003) observed no abnormalities in aged dogs resulting from short-term inhalation of transition metal aerosols (at $50 \mu\text{g}/\text{m}^3$) on heart rate, HRV, or ECG waveforms, despite their pre-existing cardiac abnormalities.

Recent animal evidence demonstrates that PM exposure can alter heart rate. Reduced heart rate was observed in myocardial-infarcted rats intratracheally instilled with 2 mg $\text{PM}_{2.5}$ (Kang et al., 2002), in aged mice exposed for 3 d to fine mode CB with an average concentration of $160 \pm 22 \mu\text{g}/\text{m}^3$ (Tankersley et al., 2004), and in studies with SH rats following nose-only inhalation of $\sim 73 \mu\text{g}/\text{m}^3$ CAPs for 4 h (Nadziejko et al., 2002) or acute instillation of an oil-combustion-derived PM (HP-12) at 3.33 mg/kg (Wichers et al., 2004a). Contrasting with these data, Wellenius et al. (2004) found a CAPs-induced increase in heart rate in a subgroup of rats with a high number of pre-exposure ventricular premature beats after a 1-h exposure to a median concentration of $350.5 \mu\text{g}/\text{m}^3$, and Harder et al. (2005) reported a mild but consistent increase in heart rate (4.8%) in rats exposed to carbon UFPs for 24 h (38 nm, $180 \mu\text{g}/\text{m}^3$). Chang et al. (2004) observed that exposure to CAPs collected in Taipei (mean $\text{PM}_{2.5}$ concentration of $202 \pm 68.8 \mu\text{g}/\text{m}^3$ in spring and $141 \pm 54.9 \mu\text{g}/\text{m}^3$ in summer) increased heart rate and mean blood pressure in four nose-only exposed SH rats compared with pre-exposure baseline and filtered air control data, while QA interval was decreased, a sign of increased cardiac contractility. The responses during the four spring exposure days were more prominent than during the 6 summer exposure

days. In a chronic exposure study, decreases in heart rate, body temperature and physical activity were observed in ApoE^{-/-} mice over 5 months of CAP exposure (average PM_{2.5} concentration during exposure was 110 µg/m³), with maximal decreases in the last few weeks (Hwang et al., 2005). Normal healthy C57 mice displayed smaller and nonsignificant changes. ApoE^{-/-} mice also showed a significant relationship between CAP exposure concentration and short-term fluctuations in heart rate.

HRV is a measure of beat-to-beat variation believed to reflect overall autonomic control of the heart, especially parasympathetic nervous activity; a change in this parameter indicates an alteration of the balance between sympathetic and parasympathetic neural input to the heart. Reduced HRV is generally interpreted as a decreased ability to respond to changes in the environment and is associated with dysfunction and disease. The standard deviation of the intervals between normal beats (SDNN) is a time domain indicator of HRV, and the square root of the mean squared differences of successive R-R (inter-beat) intervals (RMSSD) is a variant of this parameter. Recent *in vivo* studies have found evidence that exposure of animals to PM causes alterations in HRV. Harder et al. (2005) found a significant decrease in HRV in rats exposed for 24 h to carbon UFPs (38 nm, 180 µg/m³). There was no evidence of an inflammation-mediated prothrombotic state due to particle exposure; rather, the authors suggested that the timing and transient character of the response pointed to a particle-induced alteration of cardiac autonomic sympatho-vagal balance mediated by pulmonary receptor/neural pathway activation. Rivero et al. (2005a) reported a reduction of SDNN in rats at 60 min postinstillation of 50 µg PM_{2.5} collected in São Paulo, Brazil. Tankersley et al. (2004) found that a 3-d exposure of terminally senescent mice to fine mode CB at an average concentration of 160 ± 22 µg/m³ led to increases in both SDNN and RMSSD.

As part of a series of collaborative chronic inhalation studies by researchers at New York University (NYU), HRV parameters were examined in mice chronically exposed for 6 months to CAPs collected at Tuxedo, NY, with an average PM_{2.5} concentration of ~110 µg/m³ (Chen and Hwang, 2005). In ApoE^{-/-} mice, SDNN and RMSSD showed a gradual increase during late afternoon and overnight for the first 6 weeks, a decline for about 12 more weeks and then a slight turn upward at the end of the study period. In normal healthy C57 mice, there were no chronic effect changes of SDNN or RMSSD in the late afternoon, and a slight increase after 6 weeks for the overnight period. The authors suggested that the response patterns of ApoE^{-/-} mice (initial enhancement and later depression of HRV parameters) indicated a perturbation of the homeostatic autonomic function in the cardiovascular system. The heart rate and HRV data collected during the integrated NYU chronic CAP study were investigated for associations with PM_{2.5} components for three different daily time periods: during exposure, the afternoon after exposure and late at night (Lippmann et al., 2005). For decreases in heart rate there were significant transient associations with resuspended soil (RS) during exposure and with secondary sulphate (SS) in the afternoon following exposure. For decreases in HRV there were comparable associations with RO in the afternoon after exposure and with both RS and SS late at night. Further work was aimed at determining the most influential components of the elemental composition for each day (Lippmann et al., 2006). The average Ni concentration during the study was 43 ng/m³, but for 14 d there were peaks of ~175 ng/m³ and unusually low PM_{2.5} and V concentrations, associated by back-trajectory to a remote Ni point source to the northwest (Sudbury, ON). Ni was significantly associated with acute changes in heart rate and its variability in mice.

Rhoden et al. (2005) reported that intratracheal instillation of urban dust particles (SRM 1649, 750 µg) in healthy rats increased heart rate immediately post-exposure and elevated HRV during the recovery phase compared with controls, while also significantly increasing cardiac oxidant levels measured as organ chemiluminescence or thiobarbituric acid-reactive substances

(TBARS). Pretreatment with the antioxidant N-acetylcysteine (NAC) prevented PM-induced oxidative stress and prevented PM-dependent changes in heart rate and HRV. To investigate the role of the autonomic nervous system, rats were treated with sympathetic or parasympathetic blockers immediately prior to a 5-h inhalation of Boston-area CAPs at $700 \pm 180 \mu\text{g}/\text{m}^3$. Both antagonists effectively prevented CAP-induced cardiac oxidative stress. Together these data suggest that autonomic signals play a role in PM-induced cardiac oxidative stress, which was associated with significant functional alterations in the heart.

In other studies of direct heart effects, pretreatment of SH rats with ambient particles (intratracheal instillation of EHC-93 at 10 mg/kg) or endotoxin adversely affected the ability of the isolated heart to recover after an ischemic insult caused by coronary occlusion, although no difference in pathological damage was observed (Bagate et al., 2006b). The reduced recovery was mainly seen in left ventricular developing pressure (LVDP) and was observed in hearts isolated at 4 h post-exposure compared with saline-instilled animals. Healthy non-SH rats were not used for comparison in this study. Soluble components in the PM preparation and Zn as the main soluble metal in the PM also elicited a depression of LVDP (other metals were not tested). *In vitro*, Graff et al. (2004) exposed rat cardiac myocytes to noncytotoxic concentrations of Zn and V and found significant reductions in spontaneous beat rate (which corresponds to heart rate *in vivo*), as well as gene expression of certain ion channels and sarcolemmal proteins related to the electrical remodelling and slowing of spontaneous beat rate, with Zn having the greater effect.

Table 14.5 Qualitative summary of particle effects on the cardiovascular system in animal toxicology studies

Endpoint / Mechanism	Animal Models	Particle Types	Exposure Range	Effects
Tissue injury and inflammation	Mice, rats	Urban PM _{2.5} , ROFA, metal compounds	85–10000 $\mu\text{g}/\text{m}^3$ (inhalation) 100 μg (instillation)	Increased coronary and renal arteritis; myocardial inflammation and degeneration
Atherosclerosis	ApoE ^{-/-} mice, ApoE ^{-/-} LDLr ^{-/-} mice	CAPs	85–110 $\mu\text{g}/\text{m}^3$ (inhalation)	Enhanced atherosclerotic lesions in the aortic regions; increased plaque cellularity; increased macrophage infiltration, ROS generation, iNOS expression, lipid content and 3-nitrotyrosine in plaque and aortic sections
Hemodynamics and blood coagulability	Hamsters, rats, mice, SH rats	CAPs, ultrafine polystyrene particles, silica particles, electrostatic precipitator particles, EHC-93, road tunnel dust, ROFA	144–3720 $\mu\text{g}/\text{m}^3$ (inhalation) 0.1–500 μg (instillation)	Enhanced vascular thrombosis; elevated plasma fibrinogen concentrations; upregulation of genes involved in coagulability and cardiovascular function; two studies found no evidence of a particle-induced prothrombotic state
Vascular function	Rats, ApoE ^{-/-} mice	CAPs, urban particles, ROFA, industrial PM _{2.5} , traffic particles	37–733 $\mu\text{g}/\text{m}^3$ (inhalation) 100–2000 μg (instillation)	Vasoconstriction and/or impaired vasodilation; decreased L/W ratios; elevated expression and plasma concentration of vasoconstriction mediators (e.g. endothelin, asymmetric dimethylarginine); decreased

Endpoint / Mechanism	Animal Models	Particle Types	Exposure Range	Effects
				expression of eNOS
Heart function	Rats, mice, dogs, SH rats, ApoE ^{-/-} mice	CAPs, industrial PM _{2.5} , gasoline engine exhaust, oil combustion PM, CB, carbon UFPs, urban PM _{2.5} , SRM 1649 urban dust, EHC-93	60–700 µg/m ³ (inhalation) 50–2000 µg; 3.33–10 mg/kg (instillation)	Increased frequency of arrhythmias and ECG waveform abnormalities; altered heart rate, HRV, SDNN and RMSSD (both elevations and reductions); exacerbation of myocardial ischemias during coronary artery occlusion and reduced recovery from ischemic insult; increased heart tissue oxidants; some evidence of no effect on arrhythmia frequency, heart rate, HRV or ECG waveforms

14.3.3 Lung Injury and Inflammation

14.3.3.1 In Vivo Studies of Lung Injury and Inflammation

Most experimental animal studies reviewed in the 1999 PM SAD were restricted to well-defined particle species that were not directly comparable to the complex ambient particle mixture, and generally used mass concentrations well above those occurring in the environment. Pulmonary exposure to particles was noted to elicit a number of interrelated histological and cellular disturbances, including inflammation of the respiratory tract, increased AM number and activity (although these could be reduced by more cytotoxic particles), biochemical changes associated with AM activation or fibrosis, and morphological changes such as epithelial hyperplasia, lipoproteinosis, and collagen formation and fibrosis. The literature on pulmonary inflammation available at the time focused on the influx of neutrophils to the alveolar surface and expansion in size of the AM population induced by particle deposition in the alveoli. The molecular changes behind these effects were not well understood, but it was posited that increased tissue levels of molecular mediators such as IL-1, TNF- α and fibronectin correlated with exposure.

Links between particle composition and toxicity had not been thoroughly examined at the time of the 1999 PM SAD, but it was stated that the components most likely to induce acute adverse effects included metals, organics, acids and acidic sulphates, possibly occurring as coatings on fine or ultrafine carrier particles. It was recognized that particles in the fine mode were more likely to induce acute adverse effects than larger particles, and that ultrafines may be important, although data were limited. Some evidence suggested that particles in the fine size fraction or larger having little intrinsic toxicity became toxic when particle size was small enough (MMAD <0.05 μm), and that the induction of inflammatory mediators from macrophages (such as chemotactic factors) may be a function of particle surface area interacting with the receptors of AMs. Reductions in lung clearance rates were observed in conjunction with the increased AM population that accompanied high lung burdens of poorly soluble particles, indicating compromised AM-mediated alveolar clearance. The 1999 PM SAD concluded that this effect, known as “particle overload,” occurred only after chronic exposure of experimental animals to inhaled concentrations of several milligrams per cubic metre and was not expected to occur at ambient concentrations of <200 $\mu\text{g}/\text{m}^3$.

With continued research a broader PM toxicology database was available for the US EPA 2004 PM AQCD, which cited studies pointing towards the association of lung injury and inflammation with pulmonary exposure to complex combustion-related PM materials. Metals were among some ambient PM constituents identified as contributors to these effects. For example, the toxic effects of ROFA were found to be caused largely by its high content of soluble metals, including Fe, Ni and V, with some of its effects reproduced by equivalent exposures to the soluble salts of these metals. On the other hand, controlled exposures of animals to H₂SO₄ aerosols, acid-coated carbon, and sulphate salts caused little lung injury or inflammation, even at high concentrations. The US EPA 2004 PM AQCD noted that inhalation exposures of several species (rats, hamsters, dogs) to CAPs for 1–6 h/d for 1–3 d induced some signs of lung inflammation in healthy animals and enhanced inflammatory responses in chronic bronchitic rats at CAP concentrations in the range of ~100–1000 $\mu\text{g}/\text{m}^3$. Inflammatory responses were most evident at the ~200–700 $\mu\text{g}/\text{m}^3$ concentration range.

Recent studies continue to characterize particle-induced lung injury in experimental animals. Effects such as increased cellularity, protein content, and LDH activity in BALF are widely used biomarkers for lung injury, and a substantial number of recent studies have documented the commonality of these effects amongst different particle types. These particle types include CAPs (Godleski et al., 2002; Gurgueira et al., 2002; Smith et al., 2003; Lei et al., 2004a, 2004b; Rhoden et al., 2004; Schins et al., 2004; Cassee et al., 2005); ambient urban PM (Prieditis and

Adamson, 2002; Walters et al., 2002; Dick et al., 2003b; Gerlofs-Nijland et al., 2005; Pradhan et al., 2005; Mutlu et al., 2006; Seagrave et al., 2006); ROFA (Hamada et al., 2002; Lewis AB et al., 2003; Roberts et al., 2003, 2004a; Antonini et al., 2004; Hollingsworth et al., 2004; Medeiros Jr. et al., 2004; Costa et al., 2006); metal particles (Ress et al., 2003; Zhou et al., 2003b; Zhang et al., 2003; Tong et al., 2006) and other artificial particles such as CB and TiO₂ (Höhr et al., 2002; Wilson et al., 2002; Dick et al., 2003a; Bermudez et al., 2004; Gilmour et al., 2004c; Renwick et al., 2004; Chang et al., 2005b; Elder et al., 2005; Harder et al., 2005; Shwe et al., 2005; André et al., 2006; Carter et al., 2006; Stoeger et al., 2006). The majority of these studies used acute exposures.

Recent literature has also added to the evidence base characterizing the molecular mechanisms underlying the proinflammatory effects of PM, which are believed to be mediated by phosphorylation-dependent cell signalling, including extracellular signal-regulated kinases (the ERK/MAPK pathway) and the regulatory signalling cascade of the transcription factor nuclear factor kappa B (NF-κB). These pathways lead to the activation of cytokines such as TNF-α, macrophage inflammatory protein (MIP)-2, monocyte chemoattractant protein (MCP)-1 and various interleukins (IL-1β, IL-6, IL-8, IL-10). *In vivo* evidence supporting a role for these mediators following pulmonary exposure of rodents to a variety of particle types is found in recent literature (Godleski et al., 2002; Höhr et al., 2002; Seagrave et al., 2002; Dick et al., 2003a, 2003b; Zhang et al., 2003; Zhou et al., 2003a, 2003b; Roberts et al., 2003, 2004a; Schins et al., 2004; Gilmour et al., 2004a, 2004c; Lei et al., 2004a, 2004b; Chang et al., 2005b; Gerlofs-Nijland et al., 2005; Shwe et al., 2005; André et al., 2006; Carter et al., 2006; Stoeger et al., 2006). Most of these studies assessed acute effects, although several found similar increases in inflammatory markers following long-term exposures.

Recent *in vivo* studies have examined the relationship between particle characteristics, such as composition and size, and lung damage. Godleski et al. (2002) reported that inflammatory changes in rats resulting from short-term exposure to CAPs (3 d, 5 h/d) varied between experiments with CAPs collected on different days. The mean CAPs mass concentration for all exposure days was 262.21 µg/m³ (range 73.5–733 µg/m³), and the mean (± SD) particle size was 0.27 ± 2.3 µm. The observed variation in response was related to specific particle constituent concentrations. Br and Pb were useful markers of traffic-derived particles, and EC and OC were good markers for combustion processes in general; these components were significantly associated with increased neutrophils in exposed rats. By contrast, changes in lymphocytes, macrophages and other bronchoalveolar lavage fluid (BALF) measurements were not significantly related to particle mass as a binary term, nor were they associated with any of the particle components.

Evidence for PM toxicity varying as a function of location and season comes from a study by Seagrave et al. (2006) in which rats were intratracheally instilled with equivalent masses of PM_{2.5} (0.75–3 mg/rat) from sites in the southeastern US. Samples from Birmingham, AL, Atlanta, GA, Pensacola, FL, and Centreville, AL, were collected during two seasons (winter and summer) for toxicity testing and for chemical analysis and chemical mass balance-based source apportionment. Samples were also collected downwind from a series of prescribed forest burns. The winter samples from the two more urban/industrial sites (Birmingham and Atlanta) produced the greatest toxicity as evaluated in assays for inflammatory and cytotoxic potency in lung lavage and tissue. The ambient composition for the sites from which the most potent samples were collected included higher levels of EC, *n*-alkanes, hopanes and steranes, and NO₃⁻. However, NO₃⁻ was not detectable in the winter extracts, so it likely did not contribute to toxicity. PAHs were also elevated in both Birmingham samples. Source apportionment suggested that the most potent samples included more PM_{2.5} from diesel and gasoline exhaust. Projection-to-latent-surfaces analysis supported the impact of these emissions, and also indicated that

sulphate, secondary organic aerosols, meat cooking and vegetative detritus were not correlated with biological responses. Wood burning was only weakly correlated with toxicity endpoints.

Wilson et al. (2002) reported that intratracheal instillation of 125 µg ultrafine CB induced neutrophilic inflammation in the rat lung, while instillation of 100 µM FeCl₃ had no significant effect compared with controls. Coinstallation of both UFPs and FeCl₃ resulted in a potentiative neutrophil influx compared with either exposure alone. Interestingly, UFPs and metals interacted by chemical potentiation in a cell-free environment to generate ROS, but potentiation between UFPs and metal salts was not observed in macrophages *in vitro*. Fe may have been sequestered or chelated intracellularly, as suggested by results showing that J774 macrophages were able to remove Fe from cell culture medium. Thus the *in vitro* result did not predict the whole animal response to co-exposure. Zhou et al. (2003a) found no changes in BALF cellularity, protein levels or lactate dehydrogenase (LDH) activity in rats exposed to soot particles at 250 µg/m³, Fe at 57 µg/m³, or a combination of Fe and soot. However, when 45 µg/m³ of Fe was combined with soot, resulting in a total mass concentration of 250 µg/m³, other parameters were affected following inhalation, including significant pulmonary ferritin induction, oxidative stress, elevation of IL-1β and cytochrome P450s, and activation of NF-κB. In another study, four different types of UFPs were found to produce varying effects in rats. Dick et al. (2003a) observed that instillation of 125 µg Co or CB UFPs induced significant neutrophil influx at 4 and 18 h postinstillation and an increase in MIP-2 and γ-glutamyl transpeptidase levels in BALF. Nickel UFPs induced significant neutrophil influx at 18 h only, while TiO₂ UFPs did not produce significant effects.

Metal composition and solubility differences between soluble and insoluble fractions of particle samples have been analyzed as determinants of toxicity. Prieditis and Adamson (2002) studied the relative toxicities of metals present in EHC-93 urban particles and found that soluble Zn and to a lesser extent Cu intratracheally instilled in mice at the same concentration could induce lung epithelial injury and inflammation equivalent to that observed with exposure to the urban particulate sample. By contrast, other metal contaminants, such as Fe, Ni and V, caused little or no lung toxicity at the same concentration. Antonini et al. (2004) examined pulmonary responses in rats intratracheally instilled with 10 mg/kg of chemically distinct ROFA samples collected from two different areas of a power plant. Precipitator ROFA was found to be more soluble and acidic than air heater ROFA, with a significantly greater mass of each measured metal. Precipitator ROFA, particularly the soluble fraction, generated a metal-dependent hydroxyl radical as measured by electron spin resonance (ESR) and caused greater inflammation and reduced lung defence against bacterial infection than did ROFA from the air heater. Somewhat contradictory results come from Lewis AB et al. (2003), who used ROFA from the precipitator of the same Boston-area power plant. They reported that despite the ability of the soluble fraction of ROFA to generate radicals, cellular oxidant production and tissue injury were observed mostly with the insoluble and total ROFA fractions following instillation of rats with the same dose level of 10 mg/kg. In another study, fly ash from western Kentucky in the fine particle range caused a moderate degree of inflammation and increased protein levels in BALF of mice following instillation—responses that were higher than those caused by fine Montana fly ash (Gilmour et al., 2004a). Western Kentucky fly ash had a higher concentration of Fe and K and a greater percentage of carbon than Montana fly ash, but lower levels of Ca, Mg, strontium (Sr), and Mn.

Particles produced by fuel combustion vary in their level of toxicity based on fuel type, vehicle and running conditions, as demonstrated in a study by Seagrave et al. (2002) in which high-emitter gasoline and diesel vehicles produced emissions with greater toxicity per unit of combined PM and semi-volatile organic fraction mass than normal-emitters following intratracheal instillation in rats (0.13–6.3 mg/rat). Toxicity as indicated by cytotoxic, inflammatory

and lung parenchymal changes per unit mass of emissions from normal-emitter diesel and gasoline vehicles was similar in both nature and potency, with TNF- α production and several indicators of cytotoxicity and oxidative stress slightly greater for diesel. In further study, partial least-squares regression analysis revealed that lung toxicity responses in rats were most strongly associated with particulate OC, select thermal fractions of the carbon analysis, and the hopane and sterane classes of compounds from motor vehicle emission samples from “normal” and “high-emitting” gasoline and diesel light-duty vehicles (McDonald et al., 2004). Hopanenes and steranes are found in crude oil and are emitted as part of the crankcase oil emissions, and high-oil-burning vehicles show large amounts of particle-phase OC; these compounds may therefore contribute strongly to the inflammatory effects of inhaled emissions from high-emitting vehicles. Metals and PAHs showed little or no correlation with lung responses.

Stoeger et al. (2006) conducted a dose–response assessment of six different types of carbonaceous UFPs to determine which of three commonly accessible parameters—organic content, surface area or particle size—was most useful for characterizing lung inflammatory potency. Mice were intratracheally instilled with doses ranging from 5 to 50 μg and BALF was analyzed 24 h post-exposure. Smaller particles had higher proinflammatory potency than larger ones at comparable doses, while no strong correlation between OC and inflammatory measures was found. Particle surface area was found to be the most appropriate parameter for evaluating inflammatory potential, particularly a measurement developed by Brunauer, Emmet and Teller that integrates number concentration and structural geometrical features of particles such as primary particle size and ultrastructural surface properties. A particle surface area threshold below which no acute proinflammatory responses could be detected in healthy mice was identified at an instilled dose of $\sim 20 \text{ cm}^2$.

The influence of particle size on toxicity has been explored in many recent studies. UFPs are generally found to cause greater lung injury and inflammatory responses than larger size fractions, and this propensity may be related in part to their much larger surface area and PN per unit of mass, which provides a broader interface for reactions between surface agents and biological targets such as cells and proteins (Kreyling et al., 2004). In a study with Ni particles, Zhang et al. (2003) observed that instilled UFPs ($\sim 20 \text{ nm}$) were more toxic to the lungs of rats than larger Ni particles (average diameter $5 \mu\text{m}$), as shown by indicators of lung injury and inflammation in BALF. Gilmour et al. (2004a) reported that coal fly ash UFPs were more toxic to mice than fine or coarse particles taken from the same combustion aerosol, producing a higher degree of neutrophil inflammation, TNF- α induction and LDH activity following intratracheal instillation. This toxicity was associated with a greater abundance of sulphur and several trace elements (V, Cu, Se, barium (Ba), Sr, etc.) and lower levels of others (Al, Ti, Si, Fe and Mg) in the ultrafine compared with the fine and coarse fractions, although a large proportion of the mass was unidentified.

In another study, inhalation of CB UFPs caused a small but consistent significant proinflammatory effect in rats that was larger than the effect from a similar concentration of fine particles (Gilmour et al., 2004c). UFPs of CB and TiO_2 were found to induce greater neutrophil recruitment, epithelial damage and cytotoxicity than their fine counterparts in rats following intratracheal instillation (Renwick et al., 2004). In general, ultrafine CB was more toxic than ultrafine TiO_2 . Both ultrafine and fine particles significantly impaired the phagocytic ability of AMs, but only UFPs significantly enhanced the sensitivity of AMs to the chemotaxin C5a. The effects of CB UFPs with diameters of 14 or 95 nm were compared by Shwe et al. (2005) following their intratracheal instillation in mice. Repeated instillation of 14 nm particles caused a significant and dose-dependent increase in total cell numbers and specific cell types such as macrophages, lymphocytes and neutrophils in BALF, greater deposition of particles in the mediastinal lymph nodes, increased IL-6, IL-1 β and TNF- α in BALF, and increased CCL-3

mRNA expression in the lungs and mediastinal lymph nodes. These effects were greater than those caused by 95 nm particles. Elder et al. (2005) reported that compared with high surface area CB (14 nm), inhalation of CB with 8-fold lower surface area (70 nm) at 50 mg/m³ was found to result in similar mass burdens in rats at the same dose but was less potent, clearing in a similar fashion and with similar inflammatory and histopathological effects as high surface area CB at the lower dose of 7 mg/m³.

In contrast to the results above, one recent study found that coarse particles were more toxic than fine fraction particles. Schins et al. (2004) reported that on an equal mass basis, instilled coarse (but not fine) PM samples from both an industrial and a rural site in Germany induced an inflammatory reaction in rat lungs. This reaction was characterized by neutrophilic inflammation in the absence of any severe pulmonary toxicity, as indicated by the lack of increased lavage protein and LDH levels. The rural sample of coarse PM induced the most potent inflammatory reaction, significantly increasing TNF- α content as well as depleting glutathione (GSH) in BALF. Neither sample of fine PM was able to elicit significant inflammation in this model despite their higher metal content. Both coarse PM suspensions had a markedly higher endotoxin content when compared with the fine PM suspensions, which appeared to parallel the cytokine-releasing potency of the PM samples in whole blood.

Species specificity in inflammatory responses is evident in recent studies that show rats are more susceptible than mice, while hamsters appear to be most resistant to the effects of PM, possibly related to more efficient clearance and antioxidant mechanisms (Bermudez et al., 2004; Elder et al., 2005; Carter et al., 2006). Regarding route of exposure, a study by Costa et al. (2006) suggested that inhalation and intratracheal instillation may not produce equivalent responses across endpoints. Instillation of ROFA in rats at an inhalation-equivalent dose of 110 μ g mimicked inhalation (~12 mg/m³, 6 h) in terms of lobar distribution and inflammatory biomarkers over 96 h, but morphological alterations and airway hyperresponsiveness (AHR) appeared to be more dependent on the method of administration. AHR, alveolitis and epithelial hypertrophy were markedly increased following instillation but minimally affected in the inhalation group, while alveolar hemorrhage, congestion and airway exudates were pronounced post-inhalation but not prominent in instilled rats.

Genetic knockout mice, DNA microarrays and other innovative techniques are being used to study particle-induced inflammatory responses. Roberts et al. (2004a) used protein microarray and laser capture microdissection to recover airway cells and analyze the mechanisms of lung injury following intratracheal instillation of rats with 0.5 mg ROFA. ROFA exposure increased p-ERK:ERK and p-I κ B:I κ B, indicating activation of these pathways and suggesting changes in cell growth, transformation and inflammation within the airway. In another microarray study, André et al. (2006) used a whole body exposure system to expose mice to filtered air or carbon UFPs at 8 \times 10⁶ particles/cm³ with a CMD of 49 nm and average mass concentration of 380 μ g/m³. Particle exposure caused a minor inflammatory response, and lung histology did not indicate any pathomorphological changes. However, DNA microarray profile analysis revealed a biphasic response to particle exposure: at 4 h, mainly heat shock proteins were induced (a transient effect that may be involved in the subsequent activation of AMs). At 24 h a suite of immunomodulatory proteins, including osteopontin, galectin-3 and lipocalin-2, were upregulated in AMs and septal cells. In a study with knockout mice, Saber et al. (2005) reported that TNF was not required for the induction of inflammation by very high concentrations of DEPs and CB in mice following inhalation of 20 mg/m³ (4 d, 90 min/d). Inflammation (measured by IL-6 mRNA expression and neutrophil influx) and DNA damage were similar or even higher in TNF knockout mice than in wild-type mice.

Investigation of inflammatory mechanisms outside the standard biomarkers is found in recent literature. Mangum et al. (2004) found that osteopontin, a secreted cytokine with cell adhesive

and chemoattractant functions, was significantly expressed in a dose-dependent manner in rats subchronically exposed by inhalation to pigmentary TiO₂ particles. The effect was noted both early, during the period of initial pulmonary inflammation and later, following the development of fibrotic lung lesions. In another study, upregulation of osteopontin in BALF was found in mice following 24-h exposure to carbon UFPs at 380 µg/m³ (André et al., 2006). Chang et al. (2005b) reported that intratracheal instillation of 200 µg CB UFPs in mice caused a significant increase of vascular endothelial growth factor (VEGF) in BALF with a peak at 16 h and a strong correlation to alveolar-capillary permeability as indicated by total protein in BALF. VEGF may play a role in cell migration. Data on osteopontin and VEGF remain limited, and their relevance to particle-induced inflammation is not well understood.

14.3.3.2 *In Vitro* Studies of Inflammatory Responses and Cell Damage

In concert with *in vivo* studies on lung injury and inflammation, a growing amount of *in vitro* research using epithelial and macrophage cell lines and various particle types has continued to delineate and characterize the molecular mechanisms behind particle-induced inflammation and cell damage. A number of recent *in vitro* studies have aimed at ascertaining which specific components of PM are most important for its toxicity. For example, Reibman et al. (2002) reported that the smallest size fraction (<0.18 µm) of ambient New York City PM upregulated GM-CSF production (a 2-fold increase) in human bronchial epithelial cells, while the absence of an effect from carbon particles of similar size and the day-to-day variation in response suggested that chemical composition (but not the particle itself) was necessary for the effect. PM from Rome, Italy, was found to be consistently more potent than CB at inducing inflammatory reactions in murine RAW 264.7 cells (a mouse leukaemic monocyte macrophage cell line) (Pozzi et al., 2003, 2005). In another study, exposure of U937 human macrophages to DEPs and urban dust caused significant induction of the proinflammatory factors TNF-α, IL-8, cyclooxygenase (COX)-2, and CCAAT/enhancer binding protein β. Organic extracts were more potent than stripped particles for these effects, while stripped particles were more potent at elevating levels of C-reactive protein (CRP) and IL-6 mRNA and protein levels (Vogel et al., 2005). Möller et al. (2002) found that cytoskeletal dysfunctions in macrophages induced by urban dust were reduced by washing the particles with dichloromethane, which strips away organic components.

Particles entering the lung dissociate on the respiratory epithelial lining fluid (ELF) into both water-soluble and water-insoluble constituents, and the relative importance of soluble transition metals for the activity of PM is still under debate (Steerenberg et al., 2005). Dai et al. (2002) found that nonfibrogenic fine TiO₂ particles (0.12 µm) became fibrogenic in rat tracheal explants when Fe was added to the particle surface. The fibrogenic changes included increased procollagen gene expression and tissue hydroxyproline, along with NF-κB activation. Huang et al. (2003a) reported that cytokine production in BEAS-2B cells was significantly associated with the metal content of PM_{1.0} collected in Taiwan. IL-8 was correlated with Cr and Mn, and TNF-α was correlated with Fe and Cr. On the other hand, lipid peroxidation was correlated with carbon content. The impact of metals individually and in combination on a rat lung epithelial cell line (RLE-6TN) was investigated by Riley et al. (2003), who reported that the ranking of metal toxicity based on TC₅₀ values was: V > Zn > Cu > Ni > Fe. Interactions were observed for exposures containing multiple metals: Zn + V, Zn + Cu, and Zn + Ni. Zn appeared to diminish the negative impact of V and Cu, had an additive effect with Ni, but had no substantial effect on Fe toxicity. Evidence of an interaction between Ni and Fe comes from Salnikow et al. (2004), who found that co-exposure of human lung 1HAEO⁻ cells to these metals counteracted the production of IL-8 induced by Ni alone, while pretreatment with Fe partially protected cells from the hypoxic effects caused by Ni alone. In other studies, nano-Cu particles were more potent at inducing IL-8 production in A549 cells than nano-Ni or nano-V particles (Cheng, 2004), and

particulate samples collected in Singapore during bushfires generated more toxic hydroxyl radicals than those collected at other times, possibly due to an increased concentration of Fe and several other water-soluble trace metals (Karthikeyan et al., 2006).

Epidemiological studies reported positive associations between changes in PM levels in the Utah Valley during 1986–1988 and the respiratory health of the local population, during which time ambient PM reductions coincided with the temporary closure of an open-hearth steel mill. Pagan et al. (2003) analyzed water extracts of PM from steel mill operational (UE-86/88) and closure (UE-87) periods for their elemental composition and *in vitro* toxicity to primary rat airway epithelial cultures, as well as the effects of surrogate metal mixtures reflecting the composition of the extracts. They found that parallel epithelial injury was induced by Utah PM filter extracts and their corresponding Zn-Cu-V surrogate metal mixtures, suggesting these metals were largely mediating the acute airway effects observed after exposure to the PM-derived samples.

As part of the integrated NYU chronic CAPs inhalation study discussed in sections 14.3.2.4 and 14.3.8.1, the mass contributions of different source categories of CAPs collected at Tuxedo, NY, were estimated and the daily variations in cellular response were compared (Maciejczyk and Chen, 2005). Regional SS (characterized by high S, Si and OC) was the largest contributor to mass (65%), followed by RS (high Ca, Fe, Al and Si; 20%) and RO combustion (identified by the presence of V, Ni and Se; 2%). Other sources, largely due to motor vehicle traffic, contributed 13%. NF- κ B was selected as an indicator of cellular stress response following exposure of BEAS-2B epithelial cells to CAPs. The NF- κ B signal increase was most highly correlated with Ni and V among individual components and with the RO combustion source category.

Univariate regression and multivariate redundancy analysis were used to test for the correlation of cell viability and cytokine release with the concentrations of 40 elements, 7 ions and 8 carbon fractions in PM_{2.5} samples from soils and road surfaces collected at numerous sites in the western US (Veranth et al., 2006). The samples showed a wide range of potency for inducing the release of IL-6 and IL-8. The particles showed positive correlations between IL-6 release and the elemental and pyrolyzable carbon fractions, while the strongest correlation involving crustal elements was between IL-6 release and the Al:Si ratio. The authors did not anticipate that the strongest correlations would be with carbon fractions, because soil-derived PM_{2.5}, especially vehicle-generated road dust, is dominated by inorganic material. Total elemental concentrations (including redox-active transition metals) were weakly correlated with cell responses, but the bioavailable metal fraction was not tested separately.

Seasonal variations in particle toxicity have been studied *in vitro*. PM from Chapel Hill, NC, varied by season in its potency at stimulating the production of proinflammatory mediators and ROS in human AMs and normal human bronchial epithelial (NHBE) cells (Becker et al., 2005a). In macrophages, the October coarse PM was the most potent stimulator for IL-6 release, while July PM regardless of size consistently stimulated the highest ROS production. In NHBE cells, the January and the October PM were consistently the strongest stimulators for IL-8 and ROS, respectively, for all size fractions. Principal-component analysis on elemental constituents of PM identified two factors, Cr/Al/Si/Ti/Fe/Cu and Zn/V/Ni/Pb/Se/As; only the first factor correlated with IL-6/IL-8 release. Among the elements in the first factor, Fe and Si correlated with IL-6 release, while Cr correlated with IL-8 release.

The toxicity of urban PM₁₀ was found to change with the season in the subarctic climate of Helsinki, Finland. During the winter, PM was correlated mainly with LRT and combustion, while in the spring, particles were mainly derived from resuspension of road dust (Salonen et al., 2004). Springtime PM elicited a greater cytokine response in macrophages that was largely inhibited by an endotoxin antagonist, suggesting that PM-bound endotoxin was a highly proinflammatory constituent of springtime resuspended road dust. Winter PM was more potent

at inducing NO production as well as formation of 8-hydroxy-2'-deoxyguanosine (8-OHdG) adducts, a marker of oxidative DNA damage. A transition metal chelator did not modify the proinflammatory or cytotoxic responses. Jalava et al. (2006) sampled particles over nine periods in Helsinki, one of which was heavily impacted by LRT of wildfire smoke (the "wildfire episode"). Another period was partially impacted by wildfire smoke (the "mixed episode"), while impacts were negligible during the remaining periods, jointly named the "seasonal average." The particulate mass concentration in the accumulation size range (PM_{1-0.2}) was greatly increased during the two LRT episodes, but the contents of total and genotoxic PAHs were only 10–25% of those in the seasonal average sample. Particles collected during the wildfire and mixed episodes had substantially lower activity in mouse macrophage cytokine production than the corresponding particles of the seasonal average period. The authors suggested that the aged, long-range transported aerosol particles had lost a substantial part of their inflammatory activity in complex chemical transformation processes in the atmosphere, as compared with particulate samples having a greater portion of newly produced combustion-derived particles. However, the LRT events were associated with enhanced inflammatory and cytotoxic activities per inhaled cubic metre of air, due to greatly increased PM mass concentration in the PM_{1-0.2} size range.

The importance of particle size has also been investigated in recent *in vitro* studies. Schins et al. (2002) reported that coarse PM sampled from four polluted locations in Germany had greater *in vitro* cytotoxic and inflammatory effects in A549 epithelial cells and NR8383 rat macrophages than fine PM at equal mass, as shown by higher levels of LDH leakage, IL-8 release and NO production. Li et al. (2003) observed that in comparison with the fine and coarse fraction, ultrafine CAPs from the Los Angeles, CA, basin were the most potent at inducing expression of cellular heme oxygenase-1 (HO-1) and ROS formation and at depleting intracellular GSH in murine macrophage and human bronchial epithelial cell lines. The increased biological potency of this fraction appeared to be related to its content of redox cycling organic chemicals and their ability to localize to and damage mitochondria, as seen under electron microscopy. Barlow et al. (2005) found that only ultrafine CB caused a significant release of macrophage chemoattractant from rat alveolar type II epithelial cells, compared with fine particles and the negative control. Hetland et al. (2004) reported that the coarse fraction of ambient particles from a suburban area of the Netherlands was at least as potent by mass as fine or ultrafine fractions at inducing inflammatory and cytotoxic effects in A549 epithelial cells and primary alveolar type 2 cells. Also, a mineral-rich PM₁₀ collected from a road tunnel near Trondheim, Norway, was equally or more potent than ambient particles at inducing cytokine release in both cell types. In further work, the coarse fractions of PM sampled from several European cities were consistently more potent at inducing IL-6 and TNF- α in macrophages than the corresponding fine fractions (Hetland et al., 2005). Although higher levels of components such as PAHs and endotoxin were found in the coarse fractions, they were insufficient to explain the variation in PM-induced cytokine release.

The activating moieties for AM cytokine production in PM collected at two polluted sites in the Netherlands were found to be concentrated in coarse PM_{10-2.5} fractions from all 6 weeks of particle collection (Becker et al., 2003). The coarse fraction also inhibited phagocytosis and decreased CD11b expression to a greater extent than the fine fraction, while the ultrafine fraction did not affect these functions. Becker et al. (2005a) reported that coarse PM collected near Chapel Hill, NC, was more potent at inducing IL-6 release (but not ROS) in macrophages than was fine or ultrafine PM. The main proinflammatory response (TNF, IL-6, COX-2) to Chapel Hill PM in AMs was driven by material in the coarse fraction (containing 85–90% of stimulatory material in PM₁₀), while HO-1 expression was not affected in these cells (Becker et al., 2005b). Primary cultures of NHBE cells also responded to the coarse fraction with higher levels of IL-8 and COX-2 compared with fine or ultrafine PM. All fractions induced oxidative stress in NHBE cells, with fine PM inducing the highest levels of HO-1 expression.

Jalava et al. (2006) found that the ability of PM sampled at Helsinki, Finland, in coarse (PM_{10-2.5}), intermodal (PM_{2.5-1}), accumulation (PM_{1-0.2}), and ultrafine (PM_{0.2}) size ranges to cause cytokine production (TNF- α , IL-6, MIP-2) in mouse RAW 264.7 macrophages diminished with decreasing particle size. Size range had a much smaller impact on the levels of NO production and cytotoxicity or apoptosis. In another study, the coarse fraction of PM collected in northern Mexico City, heavily impacted by industry, was found to have a higher metal content than the fine fraction, more noticeable during November than in May (as well as containing higher levels of bacteria, fungi and endotoxin); however, a higher redox activity and carbon content were observed for the fine fraction (De Vizcaya-Ruiz et al., 2006). Osornio-Vargas et al. (2003), using a murine monocytic cell line, found major differences between the composition and effects of PM_{2.5} and PM₁₀ sampled in Mexico City: PM_{2.5} induced cytotoxicity through an endotoxin-independent mechanism possibly mediated by transition metals, while PM₁₀ (containing a high level of endotoxin) induced proinflammatory cytokine release via an endotoxin-dependent mechanism, as effects were reduced in the presence of recombinant endotoxin-neutralizing protein.

Mechanistic evidence for the involvement of proinflammatory signalling cascades and molecular mediators such as cytokines in the response to particles comes from a large and ever-growing *in vitro* database featuring an assortment of model systems. They include human epithelial cells exposed to urban PM (Reibman et al., 2002; Huang et al., 2003a; Hetland et al., 2004; Dagher et al., 2005; Garçon et al., 2006); epithelial cells exposed to carbon and metal UFPs (Cheng, 2004; Barlow et al., 2005; Kim YM et al., 2005); rat tracheal explants exposed to EHC-93 or Fe-loaded fine TiO₂ (Dai et al., 2002, 2003; Churg et al., 2005); co-cultures of AMs and epithelial cells exposed to various particle types (Fujii et al., 2002; Tao and Kobzik, 2002; Wottrich et al., 2004); epithelial cells treated with conditioned media from macrophages stimulated with urban PM₁₀ (Jiménez et al., 2002); perfused rabbit lung and ROFA (Samet et al., 2002); epithelial cells exposed to CAPs (Maciejczyk and Chen, 2005); human lung epithelial cells exposed to PM_{2.5} from soils and road surfaces (Veranth et al., 2004, 2006); and murine monocytes exposed to urban PM (Osornio-Vargas et al., 2003; Jalava et al., 2006). For example, Samet et al. (2002) used a perfused rabbit lung model (intact lung tissue devoid of blood elements) to show that ROFA induced the phosphorylation and functional activation of multiple transcription factors associated with proinflammatory responses in lung cells: NF- κ B, ATF-2, c-Jun and cAMP response element binding protein. Dai et al. (2003) reported that exposure of rat tracheal explants to EHC-93 or DEPs directly induced the expression of genes involved in fibrogenesis and airway wall fibrosis through NF- κ B- and transforming growth factor (TGF)- β -mediated mechanisms. Reibman et al. (2002) found that ambient New York City PM upregulated the production of the cytokine GM-CSF in primary culture human bronchial epithelial cells, associated with activation of the extracellular signal-regulated kinase (ERK) and p38 mitogen-activated protein kinase (MAPK) pathway.

Mechanisms underlying the involvement of AMs in the inflammatory response to particles continue to be studied (Jiménez et al., 2002; Möller et al., 2002; Monn et al., 2002; Pozzi et al., 2003; Goto et al., 2004b; Ishii et al., 2004; Santini et al., 2004; Kristovich et al., 2004; Wottrich et al., 2004; Vogel et al., 2005; Becker et al., 2003, 2005a, 2005b). Human epithelial A549 cells treated with conditioned media from macrophages stimulated with PM₁₀ from London and Edinburgh, UK, displayed increased NF- κ B and activator protein (AP)-1 DNA binding, and enhanced IL-8 mRNA and protein levels (Jiménez et al., 2002). Analysis of conditioned media revealed marked increases of TNF- α and enhanced chemotactic activity for neutrophils. These data suggested that PM-activated macrophages may amplify the inflammatory response by enhancing IL-8 release from lung epithelial cells, triggered in part via TNF- α . In another study, co-cultures of A549 cells and macrophages showed an increased sensitivity to ultrafine hematite and silicasol particles compared with monocultures with regards to cytokine production

(IL-6 and IL-8), pointing to an amplification mechanism between the cell types (Wottrich et al., 2004). Kristovich et al. (2004) treated human monocyte-derived macrophages with particulates, and then treated human arterial, microvascular or venous endothelial cells with supernatant recovered from the macrophages. Supernatants of macrophages exposed to coal fly ash and pure carbon particulates were relatively ineffective, while those from DEP, carbon/iron, or carbon-iron/fluoro-aluminum silicate particulates strongly induced adhesion molecule expression on endothelial cells, responses that were completely attenuated by antibody with blocking specificity for TNF- α . Because the only difference between carbon and carbon/iron particulates was the presence of surface Fe, these findings suggested particulate-induced oxidative stress was a contributing factor in macrophage activation and implicated redox active Fe as a determinant of particulate bioreactivity.

Mechanistic pathways involved in PM-induced cell damage have recently been investigated *in vitro*. Untreated PM1648 samples were found to induce necrosis and apoptosis in AMs, while treatment by organic extraction, acid digestion or high heat modified the particle surface composition and decreased the level of apoptosis (Obot et al., 2002). Blockage of apoptosis by polyinosinic acid or 2F8 antibody suggested that PM-mediated apoptosis was mediated by Class A Type I/II scavenger receptors (SRs), and altering the surface characteristics of PM may have interfered with recognition by SRs, resulting in decreased apoptosis. Xia et al. (2004) reported that ambient UFPs collected in Downey, CA, caused mitochondrial perturbations in RAW 264.7 cells, as shown by a dose-dependent opening of the permeability transition pore, interference with Ca²⁺-induced mitochondrial swelling, and induction of intracellular Ca²⁺ flux. DEP exerted a similar effect while artificial polystyrene UFPs did not, suggesting that these effects were mediated by adsorbed chemicals rather than the particles themselves. The third tier of the stratified oxidative stress model discussed in Section 14.3.3.3 is cell death, and the involvement of oxidative stress in PM-induced apoptosis or necrosis is supported by recent studies. For example, Upadhyay et al. (2003) found that PM collected from ambient air in Düsseldorf, Germany, caused dose-dependent reductions in mitochondrial membrane potential change ($\Delta\psi_m$), caspase 9 activation, and apoptosis in AECs. An Fe chelator and a free radical scavenger prevented these effects, while overexpression of Bcl-xl, a mitochondrial anti-apoptotic protein, blocked PM-induced $\Delta\psi_m$ and DNA fragmentation. These data implicated the mitochondria-regulated cell death pathway and generation of Fe-derived free radicals in the apoptosis and DNA damage caused by this PM. Dagher et al. (2006) showed that PM₁₀ from Dunkerque, France, induced apoptosis in L132 epithelial cells through activation of both the TNF- α -induced pathway (i.e. TNF- α secretion, caspase-8 and -3 activation) and the mitochondrial pathway (i.e. 8-OHdG formation, cytochrome c release from mitochondria, caspase-9 and -3 activation). Apoptotic events were also revealed by changes in the transcription rates of *p53*, *bcl-2* and *bax* genes, as well as DNA fragmentation.

The involvement of the vanilloid receptor and other proton-gated receptors in the cellular toxicity of particles has been explored in work by Agopyan et al. (2003a, 2003b, 2004), while Brown and colleagues (Brown et al., 2004a, 2004b) examined the involvement of intracellular calcium. These studies provide *in vitro* evidence that activation of proton-gated receptors could be a mechanism involved in particle-induced inflammation in both epithelial and neuronal cells, and that excessive calcium influx via activated vanilloid receptors could lead to apoptosis. Further, modulation of intracellular calcium signalling in macrophages may lead to expression of cytokines involved in the proinflammatory effects of particles, while impaired motility and phagocytic ability (as shown by changes in the F-actin cytoskeleton of exposed macrophages) may affect particle clearance from the lung.

14.3.3.3 Oxidative Stress and Airway Injury and Inflammation

It has been hypothesized that certain types of PM can induce oxidative stress by initiating the generation of ROS at the cellular level, and if the production of ROS is prolonged, endogenous stores of antioxidants become exhausted and cellular damage may ensue (Li et al., 2002; Xia et al., 2006). Recent evidence from experimental animal models has added support to the link between particle exposure and oxidative stress. Gurgueira et al. (2002) reported that acute exposure of rats to $300 \pm 60 \mu\text{g}/\text{m}^3$ CAPs from the Boston-area caused significant oxidative stress, determined as *in situ* chemiluminescence in the lung and heart but not liver, associated with increased lung and heart water content and serum LDH, indicating mild tissue damage. CAPs inhalation also led to increased activities of the antioxidants superoxide dismutase (SOD) and catalase in the heart and lung. Increased oxidant levels in the lung and heart were also triggered by ROFA but not by particle-free air or inert CB. In another study, inflammatory effects in rats produced by instilled UFPs were found to be consistent with the pattern of surface free radical generation, whereby ultrafine Co, Ni and CB, but not TiO_2 , caused significant increases in inflammatory markers as well as inducing a significant depletion of supercoiled plasmid DNA, indicative of hydroxyl radical ($\bullet\text{OH}$) generation (Dick et al., 2003a). Kooter et al. (2006) reported that pulmonary levels of HO-1 in SH rats followed a nonmonotonic function in response to acute inhalation of up to $3613 \mu\text{g}/\text{m}^3$ fine CAPs from Bilthoven, the Netherlands, with an optimal response at $\sim 600 \mu\text{g}/\text{m}^3$.

Inhalation of Fe UFPs at $90 \mu\text{g}/\text{m}^3$ induced markers of oxidative stress associated with a proinflammatory response in rats (Zhou et al., 2003b). A significant decrease in total antioxidant power was observed, along with significant induction of ferritin expression, glutathione-S-transferase (GST) activity, and IL-1 β levels in lungs compared with those of filtered air controls or rats exposed to Fe particles at $57 \mu\text{g}/\text{m}^3$. Kadiiska et al. (2004) found evidence that intratracheal instillation of rats with oil fly ash ($\sim 2 \mu\text{m}$, $500 \mu\text{g}/\text{rat}$) produced lipid-derived radical metabolites in lung tissue consistent with a carbon-centred radical adduct, as demonstrated by ESR spectroscopy analysis. Other experiments indicated that the ESR signal detected in the lung extracts of treated animals was produced *in vivo* and not *ex vivo* or *in vitro*. The authors proposed that metals in the oil fly ash catalyzed the formation of oxidants, which initiated lipid peroxidation in the lower respiratory tract of the animals. Pradhan et al. (2005) reported that urban PM_{10} intratracheally instilled at 2.5–10 mg in rats increased the output of lipid peroxides and dose-dependently increased the formation of reactive nitrogen species (RNS) in lung homogenates and BAL, respectively, while the lung antioxidants SOD and catalase were significantly decreased. GSH was not affected. These changes were more marked in quartz-exposed positive control animals. Kooter et al. (2005) isolated total lung RNA from SH rats 2–40 h after intratracheal instillation of EHC-93 at 10 mg/kg and found a time-dependent pattern of gene expression, with most changes occurring during the early response period (2–6 h post-exposure). During this early period 99 of 132 genes were unique and included genes involved in the oxidative stress response, such as *heme oxygenase-1*, *thioredoxin reductase 1*, *Cu*, *Zn-superoxide dismutase*, *glutathione*, and several metallothioneins and heat shock proteins. Upregulated genes also included those involved in inflammation, biotransformation, and signal transduction, and genes in the AP-1 family.

Recent *in vivo* studies demonstrate that treatment of animals with antioxidants such as NAC and the hydroxyl radical scavenger dimethylthiourea (DMTU) prior to particle exposure decreases or inhibits subsequent particle-induced inflammatory responses, supporting a role for oxidative stress in the mechanism of action (Dick et al., 2003b; Roberts et al., 2003; Rhoden et al., 2004). For example, Rhoden et al. (2004) showed that pretreatment with NAC prevented accumulation of CAPs-induced TBARS, edema, and PMN influx in the lungs of rats, and the histopathological effects found in CAPs-only exposed animals were not detected in NAC-treated

animals. Regression analysis revealed strong associations between increased TBARS accumulation and CAPs content of Al, Si and Fe.

Treatment with antioxidants has also been shown to inhibit the proinflammatory effects of particles *in vitro*, suggesting mediation by oxidative stress (Dick et al., 2003a; Nam et al., 2004; Ramage and Guy, 2004). For example, the dose-dependent I κ B degradation and NF- κ B activation in A549 lung epithelial cells induced by PM_{2.5} from Seoul, South Korea, was efficiently inhibited by pre-incubation with antioxidants or iNOS inhibitor, suggesting that NF- κ B activation by PM_{2.5} is mediated via both ROS and RNS (Nam et al., 2004). Huang et al. (2003b) reported evidence that the prooxidant and proapoptotic effects of ROFA were mediated by different mechanisms in human AMs, as the inhibition of oxidant production generated from mitochondrial sources did not inhibit apoptosis of AM, which was mediated by activation of caspase-3-like proteases and NO. Results with vanadyl sulphate (VOSO₄) suggested V played a role in the prooxidant but not proapoptotic effect. Churg et al. (2005) found that rat tracheal explants exposed to EHC-93 or Fe-loaded fine TiO₂ particles activated NF- κ B via a pathway involving the proto-oncogene *Src* and the receptor. This process did not require the entry of particles into airway epithelial cells but was dependent on the presence of Fe and generation of ROS by the dusts, implying that even brief contact of PM with a pulmonary epithelial cell surface may produce deleterious effects.

Many recent *in vitro* studies have examined the mechanisms of particle-induced ROS generation and oxidative stress using different particle types and cellular model systems. Examples include AMs exposed to urban PM, ultrafine carbon, metal or TiO₂ particles (Li et al., 2002; Dick et al., 2003a; Huang et al., 2003b; Beck-Speier et al., 2003, 2005), and epithelial cells exposed to urban PM_{2.5} (Calcabrini et al., 2004; Nam et al., 2004; Garçon et al., 2006; Soberanes et al., 2006) or ultrafine carbon (Ramage and Guy, 2004; Bitterle et al., 2006; Koike and Kobayashi, 2006). Aust et al. (2002) showed that Fe and in some cases other transition metals from a range of particle types (including coal fly ash and gasoline and diesel combustion particulates) were bioavailable (indicated by citrate-mobilized Fe) and capable of generating ROS, as measured by production of malondialdehyde from 2-deoxyribose. Particles from coal or gasoline combustion had a greater ability to produce ROS than particles from diesel combustion. The amount of Fe mobilized by citrate was inversely related to the size of particles and also depended on the source of coal. Fe from coal fly ash was responsible for inducing the iron-storage protein ferritin in cultured A549 cells. Mobilization of Fe from coal fly ash, especially the smallest particles, and generation of ROS were found to induce IL-8 in A549 cells.

CAPs from Downey, CA, were found to induce a stratified oxidative stress response in RAW 264.7 and THP-1 cells involving HO-1 expression at normal glutathione redox ratios (GSH/GSSG), which proceeded to JNK activation and IL-8 secretion at intermediate oxidative stress levels before culminating in cellular toxicity at high oxidative stress levels (Li et al., 2002). The overall responses to CAPs were lower than those induced by DEPs, and the potency of particles was ranked as DEPs > fine CAPs > coarse CAPs. HO-1 expression was positively correlated to higher OC and PAH content of fine vs. coarse PM, as well as to the rise in PAH content in coarse PM during the winter. Beck-Speier et al. (2003) reported that freshly generated carbon UFPs with high oxidative potential stimulated the 5-lipoxygenase (5-LO)-dependent pathway in canine AMs with formation of the proinflammatory leukotriene B₄, (LTB₄), stimulation of the COX-dependent pathway with synthesis of anti-inflammatory prostaglandin E₂ (PGE₂), and the nonenzymatic formation of 8-isoprostane as a marker of oxidative stress. Particles with lower oxidative potential (incubated for 24 h in phosphate-buffered saline before use) still induced the COX pathway with production of PGE₂, but not the 5-LO pathway, nor the formation of lipid peroxides.

A high degree of positive correlation was found between several PM species, including EC and OC, low molecular weight PAHs, and trace metals (lithium (Li), beryllium (Be), Ni and Zn) and the redox activity of PM in a study of the relationships between PM characteristics and redox activity of diesel and gasoline particulate emissions from passenger cars (Geller et al., 2006). Reduction of PM mass or number emission factors resulting from various engine configurations, fuel types and/or after-treatment technologies was found to be non-linearly related to the decrease in overall PM redox activity. Particle size may influence ROS generation. For example, Cho et al. (2005a) reported that redox activity was highest in the ultrafine fraction of PM collected at four sites in the Los Angeles, CA, basin compared with the coarse and fine fractions. Comparison of redox activity with chemical composition showed a reasonable correlation with EC, OC and benzo[ghi]perylene, consistent with species typically found in mobile emission sources. Koike and Kobayashi (2006) reported that the oxidative capacity of carbon nanoparticles in AMs and epithelial cells was dependent on particle size and surface area: 14 nm particles were the most potent, 56 nm particles less potent and 95 nm particles the least potent. Knaepen et al. (2004) stated that mechanistically the acellular oxidant-generating capacity of particles themselves (mostly determined by the physicochemical properties of the particle surface) should be discriminated from their ability to stimulate cellular oxidant generation (e.g. mitochondrial activation). Since particles are proinflammatory, the authors suggested that a further division needs to be made between primary (particle-driven) and secondary (inflammation-driven) formation of oxidants.

14.3.4 Experimental Allergy and PM Exposure

At the time of the 1999 PM SAD there were only limited data on the effects of PM exposure on allergic responses and interactions with antigen challenge. By the time of the US EPA 2004 PM AQCD, *in vivo* and *in vitro* studies had demonstrated that various types of PM could alter the immune response to antigen challenge, and that PM may act as an adjuvant. Studies at that time pointed toward the exacerbation of allergic AHR and/or antigen-induced immune responses by ambient PM, with both metals and DEPs implicated in these effects. ROFA was shown to enhance allergic sensitization in a number of studies, though the applicability of these findings to ambient PM was uncertain.

Many recent studies have used animal models to examine the interaction between antigens and PM exposure in the exacerbation of inflammatory and immunological components of experimentally induced allergy. Evidence that pulmonary exposure to particles enhances or aggravates the allergic and inflammatory responses of rodents to co-administered antigen has been reported for a number of different models, including those that used particles such as CAPs, urban PM or carbon UFPs with antigens such as ovalbumin (OVA), endotoxin (LPS) or staphylococcal lipoteichoic acid.

Researchers in Michigan investigated the health effects of urban air collected from a community in southwest Detroit using AirCARE1, a mobile air monitoring and exposure laboratory equipped with air pollution monitors, particulate collection devices and inhalation exposure chambers for animal toxicology studies (Harkema et al., 2004; Morishita et al., 2004). Only OVA-treated Brown Norway rats—not endotoxin-treated F344 rats or nonsensitized rats of either strain—that inhaled Detroit CAPs for 5 d in September (and not July) displayed significant increases in airway intraepithelial mucosubstances and eosinophilic inflammation compared with air-exposed control rats. Daily mass concentrations of CAPs during the exposure periods ranged from 16 $\mu\text{g}/\text{m}^3$ to 895 $\mu\text{g}/\text{m}^3$ in July and 81 $\mu\text{g}/\text{m}^3$ to 755 $\mu\text{g}/\text{m}^3$ in September, with mean concentrations of 676 $\mu\text{g}/\text{m}^3$ in July and 313 $\mu\text{g}/\text{m}^3$ in September. PM_{2.5} trace elements of anthropogenic origin including La, V, S and Mn were recovered from the lung tissue of rats following the 5-d

September exposure period, with greater amounts recovered from OVA-sensitized rats. Trace metals were not detected after the July exposure period, even though trace metal levels in CAPs during the 2 months appeared similar. The most likely sources of these anthropogenic trace elements were considered to be local industrial activity from large oil refineries located upwind from the Detroit exposure site. The authors proposed that the increased retention of CAPs-derived trace elements in the lungs of allergic animals may be due in part to impairment of both mucociliary clearance and uptake and removal by phagocytic cells. Instillation of the insoluble PM_{2.5} fraction caused mild neutrophilia in the lungs of healthy rats, while instilled total, soluble or insoluble fractions did not enhance inflammation or airway epithelial remodelling in OVA-sensitized rats, as was observed in rats exposed by inhalation. The fact that CAPs inhalation alone in non-sensitized controls did not induce inflammation suggested that fine particles deposited in the lungs were acting to promote or prolong the allergic pathways initiated by allergen exposure days earlier.

In another CAPs study, Kleinman et al. (2005) exposed OVA-sensitized mice to approximately 400 µg/m³ CAPs collected from two locations downwind from a freeway with heavy diesel traffic in Los Angeles, CA, using a mobile particle concentrator and exposure system. The average results from the overall study indicate that in mice exposed 50 m downwind from the freeway (compared with purified air-exposed control animals), CAPs enhanced T-helper type 2 (Th2) allergic responses for IL-5 (p = 0.005) and IgE (p = 0.045), supported by similar trends for IgG1 and eosinophils approaching statistical significance. Significant effects were not observed in mice exposed 150 m downwind from the freeway. There were differences in patterns of responses observed over the 2 years during which data were collected, as differences in concentrations and compositions of ambient PM across this period may have influenced results. This study did not include non-OVA-sensitized animals for comparison.

The Respiratory Allergy and Inflammation due to Ambient Particles (RAIAP) project, a European initiative, aimed to assess the role of ambient suspended particles in causing respiratory inflammation as well as induction and elicitation of respiratory allergies. Intranasal administration of PM collected from different European sites during three seasons was found to evoke an adjuvant activity with OVA in mice that differed in severity between samples and resulted in various effects: increased IgE and IgG1, peribronchial and perivascular inflammatory responses, hypertrophy of bronchiolar mucous cells, and increased numbers of eosinophils and neutrophils in BALF (Steenenberg et al., 2004b). Adjuvant activity of the PM samples was ranked Lodz > Rome = Amsterdam > Oslo. No differences were found between fine (2.35–0.12 µm) and coarse (8.5–2.35 µm) fractions, except that more severe histopathological lung lesions were induced by coarse particles. Winter PM was found to be more active for the IgE response than PM from spring and summer. There were no associations between endotoxin content and biological effects, although endotoxin content was higher in the coarse fraction. A further study ranked the adjuvant activity of PM in combination with OVA differently (Lodz > Rome > Oslo > Amsterdam); low-dose coarse PM and high-dose fine PM were closely associated with this activity, except for samples from De Zilk, the Netherlands, the negative pollution control site (Steenenberg et al., 2005). Spring and winter PM were more potent than summer PM. The water-insoluble fractions of Lodz, Oslo and Rome coarse particles showed increased immunoglobulin and pathological responses, while the water-soluble fraction of Lodz fine particles appeared responsible for the adjuvant activity. Results of particulate sample analysis for the RAIAP project demonstrated significant contrasts in PM chemical composition between cities (Casseo et al., 2003).

Another component of the RAIAP project analyzed the role of physical and chemical composition of PM collected from the four cities on the release of cytokines from cells *in vitro*, on respiratory inflammation *in vivo* and on adjuvant potency in animal models of respiratory and

systemic allergy (Steerenberg et al., 2006). Biological effects were used as the basis for grouping PM components into clusters. The clusters of traffic, industrial combustion and/or incinerators, and combustion of black and brown coal/wood smoke were associated primarily with adjuvant activity for respiratory allergy. The clusters of crustal material and sea spray were predominantly associated with measures for inflammation and acute toxicity. The cluster of secondary inorganic aerosol/LRT aerosol was exclusively associated with systemic allergy.

In other studies of urban PM, Fernvik et al. (2002) reported that bronchial hyperreactivity, specific IgE titres, number of recruited eosinophils, and fibronectin and LDH levels in BAL were increased in BP2 mice subcutaneously sensitized and intranasally challenged with a mixture of road tunnel dust and birch pollen, as compared with those immunized with pollen alone. Bronchial hyperreactivity is easily obtained in this mouse strain after a single allergenic provocation. Mice sensitized with birch pollen alone and challenged with pollen or pollen plus road tunnel dust showed the highest levels of the Th2 cytokines IL-4 and IL-5. Exposure to carbon core particles together with birch pollen failed to induce these effects. The carbon core particles used in this study mimicked the carbon core of DEPs, but with about 10 times more surface area than diesel soot. The authors concluded that in this experiment the organic phase bound to the carbon core of traffic PM probably had an important adjuvant effect in the induction of experimental allergy. Gavett et al. (2003) found that 100 µg of PM_{2.5} from the industrial city of Hettstedt, Germany, (with high levels of Zn, Mg, Pb, Cu and Ca) administered to sensitized BALB/c mice before OVA antigen challenge via oropharyngeal aspiration (equivalent to intratracheal instillation in deposition efficiency) significantly increased lung inflammation and AHR to methacholine (MCh) aerosol, as compared with mice exposed to PM from Zerbst, Germany, with lower metal content. Administration of Hettstedt PM before OVA sensitization increased IgE levels but did not cause increases in allergic airway responses after OVA challenge. Hettstedt and Zerbst PM_{2.5}, though differing to the degree in which they affected allergic airway responses, both significantly increased lung injury parameters and proinflammatory cytokines. Archer et al. (2004) found that fine urban PM collected in St. Louis, MO (PM1648) and intranasally instilled in transgenic OVA-sensitive mice specifically and dose-dependently increased airway reactivity, as indicated by increased enhanced pause (Penh). This exacerbation was not a direct response to increased neutrophil concentration, particle-bound endotoxin or nonspecific particle effects. TiO₂ particles were similar to saline controls with regard to airway reactivity. Particulate exposure or OVA alone did not induce significant inflammation; however, the PM1648/OVA and TiO₂/OVA combinations resulted in significant neutrophilia. Steerenberg et al. (2004c) used mouse strains with various deficiencies, as well as BALB/c mice pre-treated with the antioxidant NAC, to probe mechanisms of particle adjuvant activity. Histopathological lesions were significantly lower in the IL-4 knockout strain than in wild-type mice, providing evidence that IL-4 was involved in the stimulation of OVA-specific responses by EHC-93; on the contrary there was no evidence for the involvement of natural-resistance-associated macrophage protein 1 (Nramp1), NOS or ROS.

In studies with UFPs, de Haar et al. (2005) found that intranasal instillation of mice with CB UFPs at the highest dose (200 µg) induced immediate airway inflammation and was the only dose that had immune adjuvant activity, by inducing enlargement of the peribronchial lymph nodes and increasing OVA-specific production of Th2 cytokines (IL-4, IL-5 and IL-10). In another study, inhalation of carbon UFPs (119–526 µg/m³) by sensitized mice before allergen challenge with OVA exerted strong adjuvant effects on allergic airway inflammation, whereas exposure to particles during an ongoing allergic inflammation (after allergen challenge) produced only minor effects (Alessandrini et al., 2006). Inhalation of UFPs 24 h before allergen challenge caused a significant increase of BALF inflammatory cell infiltrate, protein, IL-4, IL-5 and IL-13 in sensitized mice compared with relevant controls. These adjuvant effects were both dose- and time-dependent and were still evident when particle exposure preceded allergen

challenge by as long as 4 d. The adjuvant effect of UFPs was also documented by increased mucus production, peribronchiolar and perivascular inflammation, and enhanced AHR. UFP inhalation in nonsensitized control animals had negligible effects on pulmonary inflammation. Last et al. (2004) reported that mice with allergic airway inflammation induced by OVA and exposed to an ultrafine aerosol of soot and FeO at 235 $\mu\text{g}/\text{m}^3$ displayed significantly increased airway remodelling (as indicated by goblet cell hyperplasia) compared with mice exposed to OVA alone, whereas airway fibrosis and airway reactivity did not differ.

In contrast to studies that found interactions between PM and antigen in co-exposed rodents, Barrett et al. (2003), using a canine model of allergic asthma (beagle dogs sensitized and challenged with ragweed), reported that despite the induction of low-level but nonsignificant inflammation in the lungs of allergic and nonallergic dogs, exposure to carbon UFPs did not alter airway reactivity or immune responses. The authors pointed out that the results may not be relevant for other types of UFPs, and that other allergen doses and timing, durations of particle exposure, and particle types or animal species may produce different results. Also, the administered dose of ragweed induced bronchoconstriction but only a low level of lung inflammation, which may be required to make the dogs more susceptible to particles.

Recent comparative studies with different-sized particles suggest that smaller particles have a greater effect than larger particles in aggravating antigen-related airway responses (Inoue et al., 2005, 2006a, 2006b; de Haar et al., 2006; Yamamoto et al., 2006). For example, Inoue et al. (2005) investigated the effects of two sizes of carbon UFPs (14 and 56 nm in diameter, instilled at 50 μg) on airway inflammatory and allergic responses in mice sensitized to and challenged with OVA. Both sizes of particles aggravated antigen-related airway inflammation, characterized by infiltration of eosinophils, neutrophils and mononuclear cells (MNCs) and by increased numbers of goblet cells in the bronchial epithelium. The particles also increased protein levels of IL-5, IL-6, IL-13, eotaxin, MCP-1, and RANTES (regulated on activation, normal T cell-expressed and secreted) chemokines in the lung compared with antigen alone. 8-OHdG formation was moderately induced by particles or antigen alone but markedly enhanced by particles in combination with antigen. Overall, the aggravation of inflammatory effects was more prominent with 14 nm particles than with 56 nm particles. Also, only 14 nm particles exhibited adjuvant activity for total IgE and antigen-specific IgG1 and IgE. In another study, mice were intranasally instilled with OVA alone or in combination with fine or ultrafine TiO_2 or fine or ultrafine CB (de Haar et al., 2006). When administered at the same total particle mass (200 μg), only the ultrafine particles of both types caused airway inflammation and demonstrated immune adjuvant activity, as shown by increased peribronchial lymph node cell numbers and production of OVA-specific Th2 cytokines (e.g. IL-4, IL-10). OVA-specific IgE and IgG1 levels in serum were only increased by co-exposure to ultrafine TiO_2 .

Endotoxin is a structural component of bacteria and an important environmental antigen that may interact with PM in producing adverse effects; LPS is a type of endotoxin. Elder et al. (2004b) studied aged rats pretreated with endotoxin aerosol and exposed via an on-road exposure system in New York State to aerosol (<1 μm) or filtered air for 6 h/d, 1–3 d. Particle mass concentration was estimated to be in the range of 37–106 $\mu\text{g}/\text{m}^3$, and the average daily geometric number mean particle size was 15–20 nm. Interactions between on-road particles and endotoxin were found: plasma fibrinogen concentration was reduced after 1 d of exposure, while BALF LDH, the percentage of PMNs in circulating blood, and surface expression of ICAM-1 (inter-cellular adhesion molecule 1) on BAL macrophages were elevated after 3 d of exposure. By contrast, Elder et al. (2004a) reported that inhalation of carbon UFPs at 150 $\mu\text{g}/\text{m}^3$ for 6 h did not induce lung inflammation in SH rats or aged F344 rats, but particle exposure and LPS injection increased plasma thrombin-antithrombin (TAT) complex levels (an indicator of ongoing

thrombin formation) in F-344 rats and heightened blood PMN 2,7-dichlorodihydrofluorescein diacetate (DCFDA) oxidation (a measure of intracellular ROS activity) in SH rats.

Inoue et al. (2006c) reported that challenge of mice with LPS elicited lung inflammation, as evidenced by lung histology and in the cellular profiles of BALF, which was further aggravated by combined exposure to organic chemicals extracted from fine urban PM (PM-OC, from Urawa City, Japan). On the other hand, the combination of PM-OC and LPS did not significantly exaggerate LPS-elicited pulmonary edema, and the induction of lung expression of IL-1 β , MIP-1 α , MCP-1 and keratinocyte chemoattractant by LPS was not influenced by combined exposure to PM-OC. These results suggest that the mechanisms underlying the enhancing effects of PM-OC on LPS-induced neutrophilic inflammation were not mediated via the enhanced local expression of proinflammatory cytokines. Yamamoto et al. (2006) reported that 14 nm CB caused a 2.7-fold higher induction of PMN influx in mice compared with that caused by 95 nm CB at 24 h postinstillation, despite the 15-fold difference in surface area dose, with no differences at 4 h. Lipoteichoic acid (LTA), a gram-positive bacterial cell wall component, caused acute pulmonary inflammation similar to that reported for the gram-negative cell wall component LPS when intranasally instilled alone. Levels of some proinflammatory indicators and Toll-like receptor 2 (TLR2) mRNA expression were significantly increased by co-exposure to 14 nm or 95 nm CB (125 μ g) and low-dose LTA (10 μ g) treatment compared with CB or LTA alone at 4 h postinstillation. PMN levels and production of IL-6 and CCL2 in the 14 nm CB + LTA group were significantly higher than that of the 95 nm CB + LTA group at 4 h postinstillation. By 24 h postinstillation, however, only PMN levels remained significantly higher.

Mechanisms involved in the exacerbation of asthma linked to PM exposure have been investigated *in vitro*. Becker and Soukup (2003), using a human monocyte-AM coculture system, reported that a wide size range of particles (coarse, fine, and ultrafine) from Chapel Hill, NC, were able to promote antigen presentation by monocytes, while the capability to specifically recruit CD4⁺ lymphocytes was contained only in AMs stimulated with the coarse PM fraction. They proposed that following recruitment of monocytes to the airways by particle-exposed AMs, the inflamed airways may be more responsive to provocation by allergens and microbial antigens carried on particles, as monocytes upregulate immune modulatory receptors in response to particles or a combination of particles and antigen. The concomitant recruitment of CD4⁺ lymphocytes by AMs via release of cytokines may establish conditions for immune activation in the lung parenchyma. Hamilton et al. (2004) exposed AMs from human subjects to PM_{2.5} from Houston, TX, for 24 h, isolated the cells and cultured them with autologous lymphocytes in an 11-d antigen-presenting cell assay. Exposure to PM_{2.5} as well as asbestos upregulated a Th1 lymphocyte-derived cytokine, IFN γ , and the Th2 lymphocyte-derived cytokines IL-4 and IL-13. Levels were significantly higher for the treatment compared with control cultures as a group, but there was extreme variability in responses between subjects, and individual sensitivities to different particles were also apparent. These results support the hypothesis that inhaled particles can upregulate the normal lymphocyte response to antigens in the lung by directly altering macrophage antigen-presenting activity. A study by Tamaoki et al. (2004) indicated that ultrafine but not fine CB could stimulate proliferation of human airway epithelial cells, and DNA and protein synthesis that may lead to thickening of the airway wall *in vivo*, characteristic of airway remodelling. Pretreatment of cells with Cu/Zn SOD and the NADPH (nicotinamide adenine dinucleotide phosphate-oxidase) oxidase inhibitor apocynin inhibited the growth-promoting response to ultrafine CB, suggesting a role for oxidative stress. Further experiments suggested that the growth-promoting effect was accounted for by autocrine release of membrane-anchored proheparin-binding (HB)-EGF and subsequent activation of the epidermal growth factor receptor (EGFR) and ERK cascade.

14.3.5 Lung Function and Airway Reactivity

Ventilatory effects of particle exposure in animal models summarized in the 1999 PM SAD included decreased pulmonary functional status, altered particle clearance from the lungs, changes consistent with airflow obstruction and bronchial hypersensitivity. However, studies had not provided any insight into how different sizes of the same particle affected ventilatory function, and it was unknown how long-term exposure in the range of ambient concentrations might affect lung function. The US EPA 2004 PM AQCD, noting that exposure of animals to CAPs produced minimal or no effect on pulmonary function in several studies, did not draw any conclusions regarding ventilatory parameters such as forced vital capacity (FVC), forced expiratory volume in 1 second (FEV₁), and peak expiratory flow (PEF) rate in animal models. Research has continued to move away from measures of pulmonary function towards histopathological and molecular endpoints.

As studies of traditional lung function parameters such as FVC decline, airway reactivity in response to PM exposure continues to be explored. Airway reactivity was discussed in the 1999 PM SAD mainly in relation to acidic aerosols. Results from animal studies, almost exclusively in guinea pigs, had shown that exposure to acidic aerosols led to increased bronchial reactivity, although pure sulphate aerosols had to be administered at doses of greater than 100 µg/m³ to cause this effect. It was hypothesized that the underlying mechanism appeared to be interference with normal contractile/dilatory homeostatic processes in the airways via modulation of airway receptors involved in the maintenance of airway tone, and that AHR may be of particular importance for asthmatic individuals. The US EPA 2004 PM AQCD stated that available evidence was suggestive but inconclusive with regard to increased airway reactivity being a possible mechanism of action for PM.

Two recent studies that evaluated traditional pulmonary function endpoints were identified. Gardner et al. (2004) compared changes in ventilatory and histologic parameters in normal rats and rats treated with monocrotaline (MCT) as a model of pulmonary hypertension. Breathing frequency, minute ventilation, and the ventilatory equivalent for oxygen increased in MCT- and vehicle-treated rats 24 h after instillation (8.3 mg/kg) or inhalation (15 mg/m³ for 6 h × 3 d) of ROFA and remained elevated 72 h postinstillation. Tidal volume and oxygen uptake were reduced only in MCT-treated rats after ROFA instillation. CO uptake decreased 24 h after instillation of ROFA, returning to control values in vehicle-treated rats but remaining low in MCT-treated rats at 72 h postinstillation. Wichers et al. (2004b) found significant and dose-related deficits in pulmonary function, including decreased tidal volume and increased breathing frequency, minute ventilation and Penh, along with increased BALF indices of pulmonary inflammation and injury in SH rats following intratracheal exposure of 0.83–8.3 mg/kg HP-12 particles collected from the inside wall of a power plant stack.

AHR is an important endpoint with regards to the relationship between particle exposure and asthma. As Goldsmith et al. (2002) state, there are at least two mechanisms by which particles may exacerbate asthma: indirectly, by amplifying the allergic airway inflammation central to asthma, or directly, by increasing airway responsiveness to triggers of bronchospasm. These possibilities are not mutually exclusive. Evidence for the induction of AHR in experimental animals has been reported in recent literature following exposure to different particle types, including CAPs (Goldsmith et al., 2002; Lei et al., 2004b), urban and industrial PM (Walters et al., 2002; Gavett et al., 2003), and ROFA (Hamada et al., 2002; Hollingsworth et al., 2004; Costa et al., 2006).

Recent work has examined the mechanisms involved in increased airway reactivity resulting from particle exposure. Walters et al. (2002) used complement factor 3 (C3)-deficient mice exposed to ambient Baltimore, MD, fine PM via aspiration challenge to demonstrate that C3

played an important role in the induction of AHR but not in the recruitment and influx of inflammatory cells into the airways. C3 is involved in the response of the immune system to pathogens. PM exposure resulted in significant increases of airway reactivity in wild-type but not C3-deficient mice. Immunohistochemical staining suggested that PM exposure caused increased C3 deposition in the airway epithelium, connective tissue and vascular endothelium of the airways in wild-type but not C3-deficient mice, while C3-deficient mice mounted similar inflammatory responses to particle exposure as wild-type mice. Hamada et al. (2002) reported discordance between the time course of AHR induction (which was maximal at 48 h) and pulmonary inflammation (which peaked at 12 h and resolved by 48 h) in mice exposed by inhalation to the aerosolized soluble leachate of ROFA (ROFA-s). Developmental differences in susceptibility to ROFA-s were noted, with AHR observed in 3- and 8-week-old but not 2-week-old mice. AHR induction also appeared to require an interaction between the component metals of ROFA-s, as it was reproduced by a mixture of the major metal components but not by any individual metal alone. Abrogation of the effects of ROFA-s by systemic treatment with the antioxidant DMTU supports a role for oxidant-mediated pathways in the generation of AHR.

14.3.6 Susceptibility and Compromised Animal Models

Epidemiological studies suggest that certain human subpopulations may be more vulnerable to the effects of particulate air pollution, for example asthmatics or individuals with chronic cardiopulmonary disease. Researchers have developed compromised animal models to study how the response to air pollution is altered by susceptibility factors in comparison with “normal” or healthy animals. Potential factors include age, diet, disease status, allergies, pathogenic infection and underlying genetics. Early studies with compromised animal models focused on changes to the deposition and clearance patterns of particles and relied on artificially induced lung lesions as models for human disease conditions. The 1999 PM SAD cited a number of studies examining the effects of particle exposure using animal models of emphysema, bronchitis and viral lung infection but did not draw conclusions with respect to susceptibility to PM. By the time of the US EPA 2004 PM AQCD, a growing number of compromised animal models were being studied and there were consistent results showing that older animals or animals with certain types of compromised health, either genetic or induced, were more susceptible to instilled or inhaled particles, although the increased animal-to-animal variability in these models created greater uncertainty in the interpretation of findings. Recent work continues to examine the interactions between PM exposure and host susceptibility, especially in the use of models examining the interaction of PM exposure with the pulmonary response to pathogens, and with induced or genetically modified models of compromising conditions such as hypertension, hypercholesteremia, predisposition towards atherosclerosis, and diabetes. Table 14.6 at the end of Section 14.3.6 presents a qualitative summary of susceptibility studies using compromised animal models.

14.3.6.1 Effects of PM on Host Defence and Response to Pathogens

Studies described in the 1999 PM SAD suggested that exposure to PM reduced antimicrobial defence capacity. The acute effects of particles on lung defence mechanisms against microbial infection appeared to be related to the physiochemical characteristics of deposited particles and not simply due to a particle effect. It was noted that increased susceptibility to microbial infection may result from subchronic or chronic exposure to high mass concentrations of even relatively benign dusts. Acute exposure to lower doses, as a function of both concentration and time, appeared to increase mucociliary clearance, whereas higher doses had the opposite effect, and this dose–response relationship was species dependent. Fewer studies had been performed using subchronic or chronic exposure. It was suggested that particles containing metals with

known cytotoxic properties may affect the immune system to a significantly greater degree. The US EPA 2004 PM AQCD found some evidence for an effect of inhaled ambient PM on lung defence mechanisms and inflammatory responses in animals infected with bacteria or viruses, potentially increasing the susceptibility of exposed animals to infection. PM-induced inflammation may damage the epithelial cell layer at the surface of lung tissue as well as other cells in the airway such as macrophages, resulting in the loss of tissue integrity (Kreyling et al., 2004). One potential consequence may be increased exposure to, and reduced capacity to defend against, microorganisms.

Several recent studies have examined the interaction between PM exposure and infection with pathogens. Zelikoff et al. (2003) reported that a single 3-h nose-only exposure of healthy rats to New York City CAPs with a mean concentration of 345 $\mu\text{g}/\text{m}^3$ had little effect on the pulmonary or systemic immune defence mechanisms required for host resistance to infectious pneumonia (subsequently induced by *Streptococcus pneumoniae*). The exception was the effect on pulmonary bacterial burdens, which were increased by CAPs pre-exposure but only at 24 h post-infection. However, a 5-h exposure of already-infected rats to CAPs with a mean concentration of 107 $\mu\text{g}/\text{m}^3$ both worsened the local infection and altered pulmonary and systemic immunity, significantly increasing bacterial burdens and decreasing percentages of lavageable neutrophils and proinflammatory cytokine levels compared with infected filtered-air-exposed controls. The authors suggested that CAPs may be acting to alter lung antibacterial defence mechanisms important in the handling of ongoing pneumococcal infections, rather than affecting mechanisms important for preventing initial bacterial infectivity.

Evidence supporting the hypothesis that soluble metals associated with ROFA led to increased morbidity and infectivity in animals challenged by bacterial infection is presented by Roberts et al. (2004b). Intratracheal instillation of rats with 1 mg/100 g body weight of ROFA or its soluble fraction, followed by pulmonary infection with *Listeria monocytogenes*, slowed the pulmonary clearance of bacteria and decreased survival. The insoluble fraction caused no significant effects. Upon removal of soluble metals from the soluble fraction via the metal-binding resin Chelex, survival and clearance were restored to control levels. By contrast, Steerenberg et al. (2004a) found no evidence that the Th1 response was lowered or that subsequent resistance to respiratory infection was reduced in rats infected with *L. monocytogenes* bacteria 24 h after the last of seven daily instillations of 50 μg EHC-93 or DEPs.

Respiratory syncytial virus (RSV) is a major cause of bronchiolitis and pneumonia in infants, and exposure may lead to the development of asthma in childhood. Lambert et al. (2003b) looked at whether particle exposure modulated the immune response to RSV in mice following intratracheal instillation of 40 μg ultrafine CB and, 1 d later, the virus. They found that pre-exposure to UFPs did not enhance RSV replication or significantly affect viral clearance. However, a Th2 environment may have been created in the lung by the particle-induced inflammatory milieu, promoting allergic immune responses rather than the Th1 responses necessary for microbial defence (e.g. gamma interferon cytokine production). A second part of this study examined inflammation and AHR in mice infected with RSV and subsequently exposed to ultrafine CB (Lambert et al., 2003a). Data demonstrated an interactive effect of UFPs on existing RSV infection entailing neutrophilia and exacerbation of AHR, with a synergistic effect in elevating lymphocyte numbers and chemokine expression (MCP-1, MIP-1 α). Viral clearance and replication in the lung were unaffected by CB exposure. Acute neutrophilia induced by CB instillation may have exacerbated inflammatory endpoints in RSV-exposed mice and caused an increase in both lung permeability (as measured by increased BAL proteins) and RSV-induced chemokines throughout the time course of infection, with production of chemokines such as MIP-1 α in RSV-infected AECs potentially playing an important role.

Recent *in vitro* studies have examined the mechanisms involved in the interaction between PM exposure and pathogenic infection. Fujii et al. (2003) reported that exposure of lung epithelial A549 cells to EHC-93 PM₁₀ stimulated them to produce and release a variety of proinflammatory mediators, and this response was modified in cells transfected with the gene for adenovirus E1A compared with those transfected with control plasmid. Adenoviruses are a common cause of upper respiratory tract infections. E1A attenuated the increased MCP-1 expression in response to PM, which was associated with decreased activation of the transcription factor Sp1. The authors hypothesized that E1A modulates the ability of epithelial cells to process particles leading to increased particle burden in the lung. Kaan and Hegele (2003) reported evidence that EHC-93 PM₁₀ exposure may interfere with mechanisms of RSV replication and viral-induced cytokine production in guinea pig AMs. The ability of AMs to phagocytose PM₁₀ was not affected by exposure, but RSV yield, a measure of robustness of viral replication within an infected cell, was severely decreased in PM₁₀-exposed AMs, regardless of the sequence of exposure, when compared with unexposed AMs. Exposure of AMs to PM₁₀ significantly decreased the production of RSV-induced IL-6 and IL-8, while exposure of AMs to RSV and/or PM₁₀ resulted in enhanced secretion of bioactive TNF- α compared with controls, without synergistic or inhibitory interaction of these agents on TNF- α production.

Gao et al. (2004) demonstrated a synergistic interaction *in vitro* between ROFA and infection with the mycoplasma *M. fermentans* on the release of IL-6 from human lung fibroblasts, and proposed that microorganisms may interact with PM-derived metals to synergistically activate signalling pathways that control lung cell cytokine production. In another study, urban PM samples (SRM-1648, SRM-1649 and EHC-93) were found to decrease NO₂ production in murine macrophages concomitant with pathogenic stimulation (LPS or interferon (IFN)), which correlated with reduced iNOS expression (Chauhan et al., 2004). On the other hand, PM_{2.5} from Vermillion, OH, (VERP) and cristobalite increased NO production, while TiO₂ was essentially inactive. VERP is dominated by combustion and photochemical particles, with an abundance of elements similar to those found in urban dusts but more acidic, with higher sulphate and nitrate contents. The authors noted that pathways leading to reduced NO release (resulting in lower bacterial clearance) or to enhanced NO production and cell injury may both be relevant to the health effects of ambient particles. Klein-Patel et al. (2006) reported that ROFA inhibited the ability of *in vitro* airway epithelium to increase the expression of β -defensin-2, an antimicrobial airway defence mechanism, and its bovine homologue tracheal antimicrobial peptide, in response to LPS and IL-1 β in the absence of cytotoxicity. The inhibitory activity was associated with the soluble fraction and attributed to V (V₂O₅ and VOSO₄ produced similar effects) and not Ni or Fe. Silicon dioxide (SiO₂) and TiO₂ particles did not produce the same inhibitory effect.

14.3.6.2 Pre-existing Disease and Susceptibility to PM

The US EPA 2004 PM AQCD noted that genetically predisposed SH rats exhibited greater oxidative stress and adverse cardiovascular responses compared with their normal counterparts in response to ROFA. Studies of rats pretreated with high concentrations of SO₂ to model chronic bronchitis demonstrated an interaction of CAPs with pre-existing lung injury, as shown by increased V_t and changes in cellular and biochemical markers in lavage fluid. The majority of studies using rats with MCT-induced pulmonary vasculitis/hypertension as a model of cardiopulmonary disease reported increased neutrophilic inflammation, exacerbated lung lesions, increased lung edema, alveolar thickening, and decreased phagocytosis of particles following ROFA exposure compared with normal healthy animals.

The SH rat has become the most extensively used animal model for human hypertension because of similarities in the process and character of disease development, with multigenetic factors proposed to be responsible for their disposition (Gilmour et al., 2004b). The SH rat exhibits borderline lung inflammation, as well as a number of associated systemic indicators of

heightened oxidative stress that are common risk factors found in human patients with CVD: for example, decreased antioxidant levels and higher plasma fibrinogen and blood neutrophil counts (Costa and Kodavanti, 2003). Numerous studies have been carried out with this strain in recent literature, though only a fraction used normal healthy rats for comparison. SH rats exposed by intratracheal instillation to power plant precipitator PM at 3.3 mg/kg displayed increased inflammation in the lungs compared with normotensive WKY rats, as measured by increased neutrophilia, BALF protein and LDH levels, increased plasma fibrinogen and MIP-2 mRNA expression, and greater translocation of NF- κ B in the lung (Gilmour et al., 2004b). This enhanced inflammatory response was accompanied by an increase in TLR4-mediated cell signalling, and the authors suggested that this pathway may be one mechanism involved in the enhanced susceptibility of SH rats to PM. Elder et al. (2004a) examined the interactive effects between endotoxin (LPS) exposure via intraperitoneal injection and CB UFPs inhaled at 150 $\mu\text{g}/\text{m}^3$ by SH rats (330–420 d old) and aged F344 rats (~700 d old). Plasma thrombin-antithrombin (TAT) complexes (an indicator of thrombin activation) were 6.5 times higher in SH rats than in aged F344 rats. Exposure of SH rats to UFPs alone significantly increased this response, while the effect of combined exposure to particles and LPS did not differ from controls. Results also pointed to heightened oxidative stress in BAL AMs and blood PMNs of SH rats compared with F344 rats, and SH rats displayed greater lung damage, as evidenced by higher BALF protein concentrations and RBCs/hemolyzed blood products. UFPs were found to significantly interact with LPS with respect to increasing plasma TAT complex levels in F-344 rats, and increasing blood PMN DCFD oxidation in SH rats.

Gardner et al. (2004) compared normal rats and rats treated with MCT to induce pulmonary hypertension for changes in ventilatory and histologic parameters following exposure to ROFA by intratracheal instillation (8.3 mg/kg) or inhalation (15 mg/m³ for 6 h \times 3 d). Exposure to ROFA by either route induced histologic changes such as alveolitis, bronchiolar hyperplasia, bronchiolocentric inflammation and alveolar septal thickening, as well as abnormalities in several ventilatory parameters, including breathing frequency, VE, and the ventilatory equivalent for oxygen. Many of these changes were enhanced by MCT treatment. Tidal volume and oxygen uptake were reduced only in MCT-treated rats following instillation. CO uptake decreased 24 h after instillation, returning to control values in vehicle-treated rats but remaining low in MCT-treated rats at 72 h postinstillation. The authors stated that the observed changes in ventilatory parameters indicated impaired gas transfer capacity in the lung, and suggested that ventilatory and gas-exchange abnormalities represent a potential mechanism for PM-associated cardiac outcomes revealed by epidemiology studies.

ApoE^{-/-} mice are a murine model of advanced aortic plaque used to study atherosclerosis. Although use of these hypercholesteremic mice as a model for human atherosclerosis has been criticized because of their extremely high blood cholesterol levels and rapid development of cardiovascular lesions in comparison with humans, the overall pathologic process is similar. As part of the integrated NYU chronic CAPs study, Chen and Nadziejko (2005) reported that ApoE^{-/-} mice and DK mice lacking apolipoprotein E and the low-density lipoprotein receptor (ApoE^{-/-} LDLr^{-/-}) developed extensive aortic lesions and prominent areas of severe atherosclerosis with chronic inhalation of ~110 $\mu\text{g}/\text{m}^3$ CAPs, while normal healthy C57Bl/6 mice were devoid of vascular lesions with the exception of a few small fatty streaks. In a further component of this study, decreasing heart rate, body temperature and physical activity were observed in ApoE^{-/-} mice over 5 months of CAPs exposure. A significant relationship was observed between CAPs exposure concentration and short-term fluctuations in heart rate, while normal healthy C57 mice displayed smaller and nonsignificant changes (Hwang et al., 2005). ApoE^{-/-} mice were also found to respond to chronic CAPs exposure with a greater perturbation of cardiovascular homeostatic function than did C57 mice, indicated by initial enhancement followed by a later depression of HRV parameters (Chen and Hwang, 2005). Another phase of this study

demonstrated neuropathological damage in the brains of ApoE^{-/-} mice, as indicated by a significantly reduced density of dopaminergic neurons following chronic exposure to CAPs compared with exposure to filtered air, while no significant effects were observed in normal healthy mice (Veronesi et al., 2005). In a separate study, Sun et al. (2005) reported that chronic exposure of ApoE^{-/-} mice to CAPs (mean PM_{2.5} concentration of 85 µg/m³) altered vasomotor tone, induced vascular inflammation, and potentiated atherosclerosis, changes which were exacerbated by a high-fat diet as compared with a normal one, although a normal healthy mouse strain was not included in this study for comparison. These results suggest a detrimental interaction between particle exposure and diet for cardiovascular health.

Another animal model of atherosclerosis is the Watanabe heritable hyperlipidemic (WHHL) rabbit. Exposure of these animals to EHC-93 PM₁₀ by intratracheal instillation of 5 mg twice per week for 4 weeks caused rapid release of monocytes and shortened their transit time through the bone marrow, with the transit time being faster in WHHL than in healthy control NZW rabbits (Goto et al., 2004a). Exposure to PM₁₀ also increased circulating band cell counts, a marker for bone marrow stimulation. The authors suggested that atherosclerosis increased the release of monocytes from the bone marrow, and PM₁₀ exposure accelerated this process in relation to the amount of particles phagocytosed by AMs.

Animal models of MI and diabetes have recently been investigated. Cozzi et al. (2006) studied the effects of ultrafine PM on ischemia-reperfusion injury in mice exposed to resuspended ultrafine PM collected in Chapel Hill, NC. Mice were exposed to a single intratracheal instillation of 100 µg PM and MI was induced 24 h later. Compared with animals exposed to vehicle control, ultrafine PM doubled the relative size of the MI, increased oxidative stress within the myocardium, and impaired endothelium-mediated relaxation of the aorta *ex vivo*. In another study, rats with MI and healthy control animals intratracheally instilled with 2 mg PM_{2.5} from an industrial area displayed significantly elevated concentrations of serum total endothelin, a protein that constricts blood vessels (Kang et al., 2002). However, increased numbers of endothelin receptor type A were only observed on cardiomyocytes of the infarct myocardium. Overproduction of endothelin receptors in compromised hearts could prime this organ to the burst of endothelins and associated elevation in blood pressure produced by PM exposure. These studies suggest that PM may exacerbate MI and impair recovery from ischemia-reperfusion injury.

Diabetes and PM exposure individually have been reported to be associated with increased oxidative stress, inflammation and endothelial dysfunction. Lei et al. (2005) examined streptozotocin-induced diabetic and healthy rats exposed via intratracheal instillation to 200 µg PM_{2.5} collected from a heavy traffic area near Taipei, Taiwan. PM exposure and diabetic status individually increased inflammatory markers (e.g. IL-6), endothelial dysfunction (e.g. reduced plasma [nitrate + nitrite]) as well as plasma 8-OHdG. The greatest effects were observed in diabetic rats exposed to PM. The authors hypothesized that PM may enhance the risk of CVD through interaction with diabetic complications leading to excess ROS generation and endothelial dysfunction. In an *in vitro* study, the soluble leachate of ROFA PM_{2.5} was found to alter vascular function and induce hyperreactivity preferentially in aortae from prediabetic insulin-resistant obese rats compared with lean normal rats (Proctor et al., 2006). ROFA leachate significantly increased phenylephrine-mediated contraction in obese but not lean rat aortae, and reduced ACh-mediated relaxant responses in both types, possibly due to transition metals in the leachate and mediated through vascular smooth muscle cells.

Transgenic mice with chronic lung inflammation caused by constitutive overexpression of TNF-α were used as a susceptibility model by Kumarathasan et al. (2005), who reported that exposure to a mixture of 0.4 ppm ozone and 4.8 mg/m³ EHC-93 for 4 h once per week for 12 weeks exacerbated oxidative stress in the lungs of transgenic but not wild-type mice, specifically

enhancing the rate of protein nitration as well as elevating the creatine kinase-MM isoform in serum, an indicator of muscle damage. The pollutants did not cause measurable inflammation in wild-type mice and did not exacerbate the inflammation already present in transgenic mice.

14.3.6.3 Other Susceptibility Factors

Studies of genetic susceptibility and characterization of strain-specific responses to PM were becoming more common at the time of the US EPA 2004 PM AQCD. Interstrain differences in AHR, inflammation, Fc-receptor-mediated AM phagocytosis and mortality had been demonstrated in mouse strains such as BALB/c, C57BL/6, C3H/HeJ and others in response to PM exposure. Some recent work has explored genetic susceptibility factors in the response to PM. Toll-like receptors are transmembrane receptors linked to signalling pathways that activate immune responses (Campbell, 2004). Stimulation of the receptor leads to activation of NF- κ B, a transcription factor that promotes the expression of genes involved in inflammation. The Toll-like receptor has been hypothesized to be a determinant of air-pollution-induced pulmonary injury and innate immunity. Cho et al. (2005b) identified significant interstrain variation in lung inflammation and hyperpermeability phenotypes induced by intratracheal instillation of 6 mg/kg ROFA from a Boston-area power plant. Differences in hyperpermeability and cellular inflammation between HeJ and OuJ mice pointed to a potential role for TLR4, as the former strain contains a dominant negative mutation in the *Tlr4* gene and was the most resistant to ROFA-induced injury responses. ROFA significantly enhanced transcript and protein levels of lung TLR4 in OuJ but not in HeJ mice, and greater activation of downstream TLR4 signal transduction molecules (including MYD88, TRAF6, IRAK-1, NF- κ B, MAPK and AP-1) was observed in OuJ mice prior to development of ROFA-induced pulmonary injury. Putative TLR4-dependent inflammatory genes that were differentially induced by ROFA in the two strains included those for IL-1 β and TNF- α . In contrast to these results, Hollingsworth et al. (2004) reported no observable differences in airway responsiveness or inflammatory responses to intratracheally instilled ROFA in a comparison of wild-type and TLR4-deficient mice, although the amount of instilled ROFA was very low: 0.05 μ g.

There has been limited research on other genes that may factor in the sensitivity to air pollution. Prows et al. (2003) determined sensitive and resistant mouse strains following inhalation of NiSO₄ aerosol and used quantitative trait locus (QTL) analysis to identify regions on several chromosomes linked to survival time. Complementary DNA microanalysis revealed expression changes in a number of candidate genes involved in cell proliferation, extracellular matrix repair, hypoxia and oxidative stress.

Age is a factor that may influence susceptibility to PM. Tankersley et al. (2003) found age-dependent changes in lung mechanics indicative of significant decrements in lung volume and compliance several weeks before death using aged robust mice with stable body weight and terminally senescent mice. During the period of homeostatic instability preceding natural death, senescent mice showed enhanced pulmonary permeability to soluble instilled ^{99m}Tc-DTPA particles despite a decrease in lung volume and alveolar surface area. The authors suggested that evidence of a pulmonary epithelial–endothelial barrier dysfunction in terminally senescent mice supports the hypothesis that an increase in lung permeability may be a contributing factor to increased PM susceptibility in the elderly and patients with lung disease. In a further study of heart rate regulation and HRV parameters, it was found that healthy aged mice increased cardiac sympathetic tone during a 3-d exposure to fine mode CB with an average concentration of 160 \pm 22 μ g/m³, while terminally senescent mice showed a greater particle-induced parasympathetic tone in regulating heart rate (Tankersley et al., 2004). The combined effects of terminal senescence and CB exposure acted to depress heart rate to an average of approximately 80 beats per minute (bpm) lower than in healthy mice.

Table 14.6 Qualitative summary of susceptibility studies using compromised animal models

Susceptibility	Animal Models	Particle Types	Exposure Range	Effects
Infectious disease	Rats and mice exposed to infectious bacteria (e.g. <i>Listeria monocytogenes</i>) or viruses (e.g. RSV)	CAPs, ROFA, EHC-93, ultrafine CB	107–345 µg/m ³ (inhalation) 40–50 µg; 10 mg/kg (instillation)	Increased pulmonary bacterial burden and slowed pulmonary clearance of bacteria; altered pulmonary and systemic immunity; decreased survival; promotion of Th2 over Th1 responses; exacerbation of AHR and inflammatory endpoints; one study found no evidence of lowered Th1 response or reduced resistance to respiratory infection
Hypertension	SH rats, rats treated with MCT	Industrial PM, ultrafine CB, ROFA	150–15000 µg/m ³ (inhalation) 3.3–8.3 mg/kg (instillation)	Enhanced inflammatory responses and lung damage; increased plasma fibrinogen and thrombin activation; heightened oxidative stress; enhanced ventilatory abnormalities
Atherosclerosis	ApoE ^{-/-} mice, ApoE ^{-/-} LDLR ^{-/-} mice, WHHL rabbits	CAPs, EHC-93	110 µg/m ³ (inhalation) 5 mg (instillation)	Development of extensive aortic lesions and prominent areas of severe atherosclerosis; greater perturbation of HRV parameters; trend of decreased heart rate, body temperature and physical activity; accelerated release of monocytes from bone marrow; neuro-pathological damage
Myocardial ischemia	Mice and rats with induced MI	Resuspended ultrafine PM, industrial PM _{2.5}	100–2000 µg (instillation)	Increased relative size of MI; heightened oxidative stress in the myocardium; impaired endothelium-mediated relaxation of the aorta; increased numbers of endothelin receptor type A on cardiomyocytes
Diabetes	Rats with induced diabetes	Urban PM _{2.5}	200 µg (instillation)	Enhanced inflammatory responses, endothelial dysfunction and oxidative DNA damage
Age	Senescent mice	CB, ^{99m} Tc-DTPA particles	160 µg/m ³ (inhalation) 25 µl (instillation)	Epithelial–endothelial barrier dysfunction and enhanced pulmonary permeability; depressed heart rate and greater parasympathetic vs. sympathetic tone

14.3.7 Particle Effects beyond the Cardiopulmonary System

At the time of the 1999 PM SAD, most research focused on PM's effects on the airway, believed to be the critical target for toxicity. In addition, effects on the immune system were studied and some preliminary work was suggestive of particle-induced cardiovascular effects. Research on the effects of PM on other systems was lacking. The importance of cardiovascular effects was much more greatly appreciated by the time of the US EPA 2004 PM AQCD. However, research on other systems, such as the central nervous and reproductive systems, was not identified at

that time. Investigation into these areas has progressed and Table 14.7 at the end of Section 14.3.7 presents a qualitative summary of particle effects beyond the cardiopulmonary system in animal toxicology studies.

14.3.7.1 Effects on the Central Nervous System

Recent evidence has indicated that inhaled particles may be able to distribute to the brain. Oberdörster and colleagues at the University of Rochester reported that carbon UFPs accumulated in the olfactory bulbs of rats following exposure for 6 h at $\sim 160 \mu\text{g}/\text{m}^3$ in whole body exposure chambers, and suggested a mechanism involving deposition on the olfactory mucosa of the nasopharyngeal region of the respiratory tract and subsequent translocation via the olfactory nerve (Oberdörster et al., 2004). Similarly, toxicokinetic analysis of inhaled Mn has found evidence for accumulation in the olfactory bulb and tubercle of the rat brain by the same mechanism (e.g. Dorman et al., 2002). It is also possible that UFPs may be able to reach the brain by crossing the blood–brain barrier following transport in the circulation.

As part of the NYU integrated CAPs inhalation study discussed in Section 14.3.2.4, neuropathology was examined in normal healthy C57 mice and in ApoE^{-/-} mice exposed to CAPs collected at Tuxedo, NY, for 6 h/d, 5 d/week during the spring and summer (Veronesi et al., 2005). The average PM_{2.5} concentration during exposure was $110 \mu\text{g}/\text{m}^3$. Genetically modified ApoE^{-/-} mice are characterized by elevated levels of oxidative stress in the brain, as well as a predisposition to develop atherosclerosis. Dopaminergic neurons from the substantia nigra nucleus compacta were significantly reduced (by 29%) in CAPs-exposed compared with air-exposed ApoE^{-/-} mice, and a statistically significant increase in immunocytochemically stained astrocytes was also noted ($p < 0.05$). Exposure did not significantly affect neuron density in C57 mice.

Elevated markers of inflammation in the brain tissue of animals exposed to PM have recently been reported. Campbell et al. (2005) studied OVA-sensitized mice exposed to fine ($< 2.5 \mu\text{m}$) or ultrafine ($< 0.18 \mu\text{m}$) CAPs collected downwind of a high-traffic area in Los Angeles, CA, with mean exposure concentrations of $441.7 \mu\text{g}/\text{m}^3$ and $282.5 \mu\text{g}/\text{m}^3$, respectively. Inhalation exposures were conducted for 4 h/d, 5 d/week for 2 weeks. In mice exposed to fine PM, levels of the proinflammatory cytokines IL-1 α and TNF- α were increased in the cytoplasmic fraction of the brain, and levels of the immune-related transcription factor NF- κ B were elevated in the nuclear fraction of brain tissue compared with control animals exposed to filtered air. IL-1 α and NF- κ B were also significantly increased in the brains of animals exposed to UFPs. Shwe et al. (2006) instilled 125 μg of 14 nm or 95 nm CB into the nostrils of 8-week-old mice once per week for 4 weeks. Proinflammatory cytokines (IL-1 β and TNF- α), chemokines (MCP-1/CCL2 and MIP-1 α /CCL3), and monokine-induced interferon-gamma/CXC chemokine ligand (CXCL9) mRNA were induced in the olfactory bulb but not the hippocampus of mice instilled with 14 nm CB, while changes were not induced in animals instilled with 95 nm CB or vehicle control. The authors postulated that the 14 nm particles may have translocated to the olfactory bulb via the olfactory neuron and activated microglial cells, which induced an increase in the mRNA expression of proinflammatory molecules.

Evidence of CAPs-induced changes to neurotransmitter levels in specific brain areas and modulation of neuroendocrine pathways involved in autonomic control of respiratory function and the stress axis were found in a study by Sirivelu et al. (2006). Rats with or without OVA-induced allergic airway disease were exposed for 8 h to CAPs with a PM_{2.5} concentration of $500 \mu\text{g}/\text{m}^3$ using a mobile air research lab in Grand Rapids, MI, with control animals exposed to filtered air and treated with saline. Changes in neurotransmitters were observed in the olfactory bulb and discrete areas of the hypothalamus, such as the paraventricular nucleus (PVN), arcuate nucleus (AN) and medial preoptic area (MPA), while neurotransmitter concentrations in

other areas of the hypothalamus and brain remained unchanged, suggesting specificity of effects. The concentrations of norepinephrine in the PVN and olfactory bulb were significantly increased by OVA alone and by CAPs, with or without sensitization to OVA, in comparison with controls. Dopamine levels in the MPA were significantly increased in the OVA + CAPs group compared with those of the control and saline + CAPs groups. Exposure to CAPs also increased circulating levels of corticosterone, paralleling the increase in norepinephrine levels in the PVN, which may indicate activation of the hypothalamo-pituitary-adrenal axis or stress axis.

14.3.7.2 Developmental and Reproductive Effects

Developmental and reproductive endpoints continue to receive little attention in experimental animal research on the health effects of PM. In one recent study, the rate of cell proliferation in the regions arising immediately beyond the terminal bronchioles (the proximal alveolar region) of 10-d-old rat pups exposed for 6 h/d over 3 d to an aerosol of soot and Fe particles was significantly reduced in exposed neonates compared with filtered-air-exposed controls (Pinkerton et al., 2004). The particles fell in the size range of 10–50 nm, with a mean mass concentration of $243 \pm 34 \mu\text{g}/\text{m}^3$ and an average Fe concentration within the aerosol of $96 \mu\text{g}/\text{m}^3$. There was no effect on the rate of cell proliferation within terminal bronchioles or the general lung parenchyma. These results provide evidence that exposure to airborne particles during the neonatal period may affect lung growth by altering cell division at critical sites of the respiratory tract, suggesting a mechanism for the impaired growth in lung structure and function observed in air-pollution-exposed children in epidemiological studies (see Section 14.8.2.3). Hamada et al. (2002) reported developmental differences in the susceptibility of mice to the aerosolized soluble leachate of ROFA. AHR was observed at 48 h following pulmonary exposure in 3- and 8-week-old but not 2-week-old mice.

Mussali-Galante et al. (2005) observed that inhaled V ($1436 \pm 225 \mu\text{g}/\text{m}^3 \text{V}_2\text{O}_5$, 1 h twice weekly for 12 weeks) time-dependently reduced the immunoreactivity of gamma-tubulin in the Sertoli, Leydig and germ cells of male mice. Alterations to this protein may affect microtubule-related functions such as cell division during spermatogenesis. V concentrations increased significantly in the testes starting with the initial inhalation exposure (compared with control animals) and remained high to the end of exposure.

14.3.7.3 Effects on Other Systems

Effects on organs and systems other than the cardiopulmonary, immune and nervous systems have not been extensively studied. However, exposure to PM may cause systemic oxidative damage detectable beyond the cardiopulmonary system, as suggested by two recent studies from China. Liu and Meng (2005) intratracheally instilled $\text{PM}_{2.5}$ from the city of Taiyuan into rats and found that at 24 h post-exposure, doses of 7.5 mg/kg and 37.5 mg/kg (but not 1.5 mg/kg) significantly increased levels of lipid peroxidation in the heart, liver, lungs and testicles; decreased Cu, Zn-SOD, catalase and glutathione peroxidase (GPx) activities in the lungs, livers, kidneys and brains; and depleted GSH levels in all measured organs compared with control animals. Meng and Zhang (2006) reported that instillation of 1.5–37.5 mg/kg of both normal weather and dust storm $\text{PM}_{2.5}$ derived from the cities of Baotou and Wuwei caused a dose-dependent decrease of SOD activities and GSH contents in lungs and livers, and a dose-dependent increase of TBARS levels in the lungs, hearts and livers of exposed rats compared with their respective controls. The effects of normal weather $\text{PM}_{2.5}$ on each examined index were greater than dust storm $\text{PM}_{2.5}$ but not significantly different.

Table 14.7 Qualitative summary of particle effects beyond the cardiopulmonary system in animal toxicology studies

Target System	Animal Models	Particle Types	Exposure Range	Effects
Central nervous system	Rats, ApoE ^{-/-} mice and normal mice, OVA-sensitized rats and mice	Carbon UFPs, fine and ultrafine CAPs, ultrafine CB	110–500 µg/m ³ (inhalation) 125 µg (instillation)	Particle accumulation in olfactory bulbs; reduced dopaminergic neurons and increased astrocyte density in the substantia nigra; elevated markers of inflammation in brain tissue (e.g. IL-1α and TNF-α); increased neurotransmitter levels in the olfactory bulb and hypothalamus (dopamine and norepinephrine); increased circulating levels of corticosterone
Reproductive system and development	Rat pups, young and adult mice	ROFA, Soot/Fe aerosol, V ₂ O ₅	243–1436 µg/m ³ (inhalation) 50 mg/ml (nebulized aerosol)	Reduced rate of cell proliferation in the proximal alveolar region of the growing lung; developmental differences in susceptibility to AHR; reduced immunoreactivity of gamma-tubulin in Sertoli, Leydig and germ cells
Other systems	Rats	Urban PM _{2.5}	1.5–37.5 mg/kg (instillation)	Systemic oxidative damage in the kidney, liver, brain and testicles as shown by altered activities of antioxidants (GSH, SOD, catalase) and increased lipid peroxidation

14.3.8 Carcinogenicity and Genotoxicity of PM

The 1999 PM SAD focused on carcinogenicity as it was investigated in terms of a “particle effect” of inert particles. The document concluded that the overall evidence at the time indicated that a number of different particle types, including TiO₂, CB, DEPs and silica, when inhaled for long periods of time at sufficient doses, could induce lung cancer in rats but not in mice or hamsters. The interpretation of experimental studies relating to the carcinogenic effects of PM for potential extrapolation to humans was unclear, given the very high particle loads required to induce a carcinogenic response in these studies. Furthermore, interpretation of these results was confounded by the necessity of using a single particle type, and by the carcinogenic potential of substances that may be adsorbed to the particle surface. The US EPA 2004 PM AQCD did not discuss the animal cancer bioassays considered by the SAD, but stated that the genotoxicity of PM found in some *in vitro* studies supported the biological plausibility of a link between long-term exposure to particles and lung cancer, as suggested by epidemiological studies. Evidence had shown that ambient PM (especially the fine fraction) possessed mutagenic properties, and studies examining the fractional mutagenicity of coal smoke and gasoline and diesel exhausts showed that the polar component was the most mutagenic, with nitro-PAH present in this fraction. Data at the time, mainly *in vitro*, suggested that both ambient PM and combustion products of coal, wood, diesel and gasoline could be mutagenic or

genotoxic, and provided some clues as to possible mechanisms underlying these effects. Exact comparisons of the mutagenic potency of combustion emissions from various sources were not possible, however, because the data provided in studies varied greatly in units in which mutagenicity was expressed, and mass or size details regarding the dose of PM extract delivered to cells were limited or missing, thus rendering difficult any quantitative extrapolation of the reported findings.

Carcinogenicity studies using environmentally relevant particles were not identified in recent literature, and there are few recent studies with other types of particle. Ress et al. (2003) studied the carcinogenicity of V, a metal often detected in ambient PM, and concluded that inhalation of relatively high levels of V_2O_5 (up to 4 mg/m^3) for 2 years was a pulmonary carcinogen in male but not female F344/N rats, and in both male and female B6C3F₁ mice. Pott and Roller (2005) examined the carcinogenicity of granular dusts in the lungs of female SPF Wistar rats following weekly intratracheal instillation of particles over a maximal period of 20 weeks until the intended cumulative mass dose was reached, which varied between treatment groups and ranged from 3 to 120 mg. Exposures began at the age of 8–9 weeks. Most treatment groups started with 48 rats, while some began with a lower number ($n = 21\text{--}40$). Nineteen dusts with varying properties were tested, including diesel soot, copier toner, CB and different coal dusts. Quartz, amorphous SiO_2 and both hydrophilic and hydrophobic TiO_2 were also tested. Sixteen of the 19 dusts formed a group for which no specific toxicity was detected as the cause of their carcinogenicity, and were defined as respirable granular bio-durable particles (GBPs) without known significant specific toxicity. All 16 GBPs produced many more lung tumours than expected. For example, tumour incidence per μl dust burden in the lung ranged from 1.1 to 4.0 $\%/\mu\text{l}$ for fine coal dusts, 3.1 to 9.4 $\%/\mu\text{l}$ for fine diesel soot, 7.6 to 22.5 $\%/\mu\text{l}$ for ultrafine CB, and 6.3 to 20.2 $\%/\mu\text{l}$ for ultrafine hydrophilic TiO_2 . GBP volume in connection with particle size turned out to be the most adequate dose metric for carcinogenicity. GBP UFPs (mean diameters of 0.01–0.03 μm) were twice as potent as GBPs in the size range of 0.09–0.2 μm and 5½ times more potent than GBPs of 1.8–4 μm .

Similarly there continues to be only a limited amount of *in vivo* research on the mutagenic effects of PM. Notable results have come out of work by researchers at McMaster University and Health Canada on the genotoxicity of ambient air pollution from an industrial site at Hamilton Harbour on Lake Ontario. Somers et al. (2002) housed groups of outbred Swiss-Webster laboratory mice at two field sites: 1 km downwind from two integrated steel mills and a major highway, and simultaneously at a rural reference site 30 km away. Following 70-d *in situ* exposures, mice were returned to an animal care facility for breeding and analysis. The heritable mutation frequency at tandem-repeat DNA loci in mice exposed at the industrial site was elevated 1.5- to 2-fold compared with those at the rural site, and this statistically significant elevation was found to be due primarily to an increase in mutations inherited through the paternal germline. HEPA filtration of ambient air significantly reduced heritable mutation rates at repetitive DNA loci in mice housed outdoors near the industrial site, while by contrast mice exposed to ambient and HEPA-filtered air at the less polluted rural site showed no differences in heritable mutations (Somers et al., 2004). Both total suspended particulate matter (TSP) and PAHs were higher at the urban-industrial site than at the rural site, and their levels were related to the daily number of hours the sampler was downwind of the industrial core area. HEPA filtration protected mice from exposure to all airborne PM save the smallest UFPs, while anywhere from 55% to 100% of particle-bound PAHs were likely removed by filtration. These data suggest that exposure to ambient PM from industrial and mobile sources may have been the main factor contributing to elevated mutation rates in sentinel mice, but the relative importance of gas-phase substances (e.g. some PAHs) in contributing to these genotoxic effects could not be determined.

In another study of exposure to ambient particles, Soares et al. (2003) reported that chronic exposure of BALB/c mice to urban air pollution in São Paulo, Brazil, elicited a significant ($p = 0.016$) increase in somatic mutations (as measured by micronuclei frequency in peripheral erythrocytes) compared with mice maintained in the countryside. Micronuclei frequency increased with aging, with the highest values obtained on the 90th d of the experiment ($p < 0.001$). The mean difference in micronuclei frequency between mice in São Paulo and Atibaia city, which had negligible levels of pollution, was correlated with the pollution levels in São Paulo during the previous week of exposure. However, a specific pollutant could not be identified as responsible for the observed effect in São Paulo; correlations were found for each of PM_{10} , NO_2 and CO, which are general markers of automotive emissions. The monthly means of these pollutants during the 120-d exposure period fell in the ranges of 31–47 $\mu g/m^3$, 97–108 $\mu g/m^3$ and 2.4–3.2 ppm, respectively.

In other recent *in vivo* mutagenicity studies, Park JH et al. (2005) used a diffusion flame system to generate fine PM that was observed to be genotoxic in B6C3F1 mice exposed to 100–400 $\mu g/m^3$ for 2–4 weeks. The frequency of splenic lymphocyte cells with chromosome aberrations was increased, and micronucleated reticulocytes were induced in a time- and concentration-dependent manner. PM derived from Fe-doped flame induced more chromosomal aberrations than non-Fe-doped flame. Saber et al. (2005) reported that inhaled CB particles (20 mg/m^3 , 90 min \times 4 d) induced IL-6 mRNA in the lung tissue, an inflammatory response that was found in both wild-type mice and mice deficient in TNF signalling (TNF $^{-/-}$ mice). The level of DNA strand breaks in BAL cells measured by the Comet assay was higher in TNF $^{-/-}$ mice than in TNF $+/+$ mice, and the results suggested that CB-induced DNA damage was independent of neutrophil infiltration. Borm et al. (2005) reported that inhalation of high concentrations of the commercial CBs Printex 90 or Sterling V at 50 mg/m^3 for 13 weeks did not result in PAH-DNA adduct formation in lung DNA compared with sham-exposed F344 rats.

While *in vivo* work in this area has been fairly limited, *in vitro* studies on the mutagenicity of PM continue to proliferate. In general, these studies have used different particle types, cell lines and assays, which can make it difficult to compare results across studies. *In vitro* mutagenic and DNA-damaging effects of PM have been recently reported under a variety of study designs. They include human AECs exposed to urban and traffic-related PM (Knaapen et al., 2002; Shi et al., 2003; Healey et al., 2005; Gutiérrez-Castillo et al., 2006); the Ames test (*Salmonella* mutagenicity assay) and PM from urban, rural and industrial sites or motor vehicle emission samples (Massolo et al., 2002; Zhao et al., 2002; Brits et al., 2004; McDonald et al., 2004; de Kok et al., 2005); the plasmid assay and urban PM (Merolla and Richards, 2005; Shao et al., 2006); human fibroblasts, human B-lymphoblastoid cells, HeLa cells and murine RAW 264.7 cells exposed to urban particles (Karlsson et al., 2004; Pedersen et al., 2004; Poma et al., 2006); human lymphocytes exposed to sand dust storm $PM_{2.5}$ (Wei and Meng, 2006a, 2006b); and human bronchial epithelial cells exposed to gasoline and diesel extracts (Pohjola et al., 2003a, 2003b).

Recent studies have compared the mutagenicity of PM from different sources, locations and seasons. Binková et al. (2003), using an acellular assay (CT DNA) combined with ^{32}P -postlabelling, found that DNA adduct patterns induced by organic compounds associated with respirable particles corresponded to similar major emission sources at three locations in the Czech Republic representing urban, suburban and rural areas. Generally higher activity was found during the winter season than in summer, and the different proportions of individual PAHs suggested traffic as a major emission source in the summer and residential heating as a major winter source at all three sites. Massolo et al. (2002), using the Ames test, observed the highest mutagenic effects in PM sample extracts from the winter when compared with the summer season in La Plata, Argentina, and Leipzig, Germany, the time of domestic heating in both

regions that corresponded with higher levels of particle-bound PAHs. The greatest mutagenic effects were observed in the urban areas of both cities and in the industrially influenced area of La Plata compared with more rural and less polluted control sites in both regions. Zhao et al. (2002) also found that winter samples of PM sampled in Shanghai, China, had higher overall mutagenic potency than summer samples using the Ames test, the rat hepatocyte unscheduled DNA repair assay and the mice micronuclei test. Similarly, PM₁₀ collected during the winter heating period in Beijing, China, with a higher content of soot aggregates and lower levels of minerals and fly ash, was reported to cause more DNA damage than PM₁₀ collected at other times in the plasmid DNA assay (Shao et al., 2006).

The mutagenicity of organic extracts of airborne PM collected at eight air monitoring sites over 2 years in southwestern Germany was investigated by Erdinger et al. (2005) using the Ames test. There was significant correlation between NO, a strong indicator of vehicle exhaust gases, and mutagenic activity, while correlations with NO₂ and SO₂ were weaker. In a study by Brits et al. (2004), PM₁₀ from an urban site in Belgium was found to be the most genotoxic in comparison with PM from industrial and rural sites, as shown by four different *in vitro* assays. Poma et al. (2006) studied micronuclei induction in murine RAW 264.7 cells and found that fine CB particles were consistently less genotoxic than fine atmospheric particles collected in an urban area of L'Aquila, Italy, suggesting that the contaminants absorbed onto the atmospheric particles were involved in genotoxicity.

Smaller-sized particle fractions are most often more highly mutagenic than larger fractions under the same conditions, as shown in recent studies (Massolo et al., 2002; Rahman et al., 2002; de Kok et al., 2005; Healey et al., 2005; Gutiérrez-Castillo et al., 2006). For example, mutagenic effects in the Ames assay were found to be associated with very fine (<0.49 µm) and fine (<1.5 µm) particle-bound compounds in PM samples from La Plata, Argentina, and Leipzig, Germany, corresponding to a higher PAH content in these fractions compared with larger ones (Massolo et al., 2002). In addition, coarser particles (0.49–3 µm) from an industrially influenced site in La Plata also exhibited high mutagenic potency. Mass concentration and mutagenic activity per unit air volume of different particle size fractions can vary by location. Kawanaka et al. (2006) found that most of the mutagenic activity as measured by the Ames test in size-fractionated PM from urban and suburban sites in Japan was in the fine particle fraction (<2.1 µm). There was almost no difference in the contribution of fine particles to the mutagenic activity of total PM between the two sites; however, there was a clear difference in the contribution of UFPs (<0.12 µm). UFPs, contributing only 2.3% to total PM mass, accounted for 5.7% of the mutagenic activity of total PM at the suburban site and as much as 12% at the urban roadside site. The mutagenic activity per unit air volume in the ultrafine fraction at the urban roadside site was 3.1-fold higher than that at the suburban site (1.2 vs. 0.38 Rev/m³), compared with only a 1.4-fold increase for the fine fraction. In contrast to studies reporting higher mutagenic potency in smaller-sized fractions, Greenwell et al. (2003) found that acellular oxidative DNA damage caused by PM from urban and industrial sites in South Wales was greater in the coarse than in the fine fraction, and Shi et al. (2003, 2006) reported that the coarse fraction of urban PM from Düsseldorf, Germany, induced significantly higher •OH generation and stronger acellular 8-OHdG induction than the fine fraction, although within A549 cells no differences in 8-OHdG induction were observed.

Some recent work has sought to determine the components of PM that are most important for its DNA damaging effects. In an indication of the number and kinds of mutagenic chemical species present in ambient PM, Pedersen et al. (2005) quantified approximately 150 organic compounds, including 31 known human cell mutagens in PM_{2.5} collected from five sites in the northeastern US. Molecular weight 226–302 amu PAHs were the most important mutagens identified with respect to potency, with the same compounds accounting for similar portions of

total attributed mutagenicity in each sample using the h1A1v2 human B-lymphoblastoid mutation assay. Known mutagens accounted for only 16–26% of the total mutagenicity of the unfractionated extracts and about 20% of that of nonpolar and semipolar fractions. The remaining mutagenicity was probably attributable to other as yet unknown semipolar and polar mutagens or to interactions among the constituents. In a study of 1950s London, UK, smog PM samples, Merolla and Richards (2005) established the following bioreactivity hierarchy based on the plasmid scission assay of surrogates of its water-soluble metal content: $\text{Fe}^{2+} > \text{Cu}^{2+} > \text{Fe}^{3+} > \text{VO}^{2+} > \text{Zn}^{2+} > \text{As}^{3+} = \text{Pb}^{2+} = \text{Mn}^{2+} = \text{VO}_3^-$. Oxidation state was important, with low-valence transition metals being the most bioreactive, and synergism was observed between Zn and various metal ions such as Cu^{2+} , Fe^{3+} and VO^{2+} .

A number of studies have fractionated PM for comparison of different extracts. Zhao et al. (2002) studied the mutagenicity of fractionated extractable organic matter from PM sampled in Shanghai, China, using the Ames test, the rat hepatocyte unscheduled DNA repair assay and the mice micronuclei test. Mutagenic potency was found primarily in the acid, aromatic and polar fractions of summer samples, while winter samples did not show clear differences between fractions. PM collected from urban and industrial sites in South Wales caused 50% oxidative degradation of DNA *in vitro* at concentrations as low as $12.9 \pm 2.1 \mu\text{g/ml}$ and $4.9 \pm 0.9 \mu\text{g/ml}$, respectively, and the primary source of this bioreactivity was found to be in the soluble fraction (Greenwell et al., 2003). Pedersen et al. (2004) found that semipolar fractions of $\text{PM}_{2.5}$ samples from five sites in Massachusetts and New York State were the most mutagenic in h1A1v2 human B-lymphoblastoid cells. The semipolar fractions were mutagenic to different degrees in each region, suggesting regional differences in the sources and/or transport and transformation of mutagenic compounds in $\text{PM}_{2.5}$. The polar and nonpolar fractions did not exhibit such variation, nor did the unfractionated extracts. The relative contribution of each chemical fraction to mutagenic potency was not related to urbanization within the regions. Karlsson et al. (2004), using the Comet assay, found that the genotoxic properties of SRM 1649 urban dust particles in cultured human fibroblasts appeared to be present in its DNA-reactive polyaromatic compounds, in its water-soluble oxidizing substances, and also in the insoluble particle core. Healey et al. (2005), using the alkaline Comet assay and the plasmid strand-break assay, observed that 75% of the damage induced by urban PM collected from a high traffic area of Leeds, UK, could be induced by its organic extract compared with whole or washed particles. PAH content was reported to be a stronger determinant of PM genotoxicity than transition metals in a study of urban PM from Maastricht, the Netherlands (de Kok et al., 2005). The concentration of total carcinogenic PAHs correlated positively with radical-generating capacity, direct and S9-mediated mutagenicity in the Ames test, and the induction of DNA adducts and oxidative DNA damage in Salmon testis DNA. The interaction between total PAHs and transition metals correlated positively with DNA-adduct formation, particularly with the $\text{PM}_{2.5}$ fraction. Gutiérrez-Castillo et al. (2006) found that although lower concentrations of PM were detected in the southwest area of Mexico City than in northern areas, southwest PM possessed a higher load of genotoxic compounds. Water-soluble transition metals and to a lesser extent organic-soluble fractions were important factors for the induction of DNA damage in the Comet assay. PM composition was shown to be a more relevant indicator than mass, and significant seasonal variation was observed, with PM from the cold-dry season (November/December) having a higher load of PAHs and metals than PM from the warm-dry season (April/May). DNA damage was actively repaired in A549 cells and essentially completely removed after 150 min of incubation, suggesting that DNA repair enzymes were not damaged by PM exposure. Somewhat contrasting with these results, De Vizcaya-Ruiz et al. (2006) reported that coarse and fine PM fractions collected in northern Mexico City, which is heavily impacted by industry, caused higher amounts of DNA damage (as assessed in THP-1 cells by the Comet assay) compared with fractions collected in the south of the city during both May and November. In

another study, the negative correlation between water-soluble trace elements (especially Zn but also Al, V, Fe, etc.) and TD₂₀ values (the toxic dose of PM causing 20% plasmid DNA damage) of PM from Beijing, China, suggested that water-soluble metals likely played an important role in the induction of plasmid DNA damage (Shao et al., 2006). PM collected during dust storms, composed mainly of coarse mineral particles and up to 5 times higher in mass, had a lower oxidative capacity than non-dust-storm particles.

The mutagenicity of particles from fuel emissions has been analyzed in recent work. Pohjola et al. (2003a, 2003b), analyzing PM and semi-volatile compounds collected from the gasoline exhaust of passenger cars, observed that reformulated and standard diesel fuel extracts formed about 11- and 31-fold more DNA adducts in human bronchial epithelial cells than gasoline extracts, respectively, when PAH-DNA adduct levels were calculated on an emission basis (adducts/mg PM/km), whereas on a particulate basis (adducts/mg PM) no difference between the diesel and gasoline extracts was found. Although PAH concentration was higher in diesel particulate extracts, DNA binding by gasoline-particulate-bound PAH compounds was more pronounced than that by diesel-particulate-bound PAH compounds. Diesel extracts exhibited higher mutagenicity in the Ames test than did gasoline extracts. The relationships between particle and semivolatile organic chemical constituents of motor vehicle emission samples and bacterial mutagenicity and lung toxicity in mice were investigated in studies by Seagrave et al. (2002) and McDonald et al. (2004). The chemicals associated with mutagenicity (such as particle-bound high molecular weight nitro-PAH compounds) were the same chemicals that have been implicated for this endpoint by decades of bioassay-directed fractionation studies, and were different from those most closely associated with pulmonary toxicity, as PAHs showed little or no correlation with lung responses.

A number of recent *in vitro* studies have focused on the mechanisms responsible for the genotoxic effects of particles. It has been hypothesized that PM has the ability to cause specific DNA adducts that form through oxidative stress pathways. The biomarker 8-OHdG is a common measure of oxidative DNA damage, and is biologically relevant due to its ability to induce G→T transversions, which are among the most frequent somatic mutations found in human cancers (Pilger and Rüdiger, 2006). Support for a mechanism of PM-induced DNA damage mediated via transition-metal-dependent oxygen radical formation is provided by a number of recent *in vitro* studies. For example, Shi et al. (2003) showed that the hydroxylation of dG to form the 8-OHdG adduct at physiological pH in calf thymus DNA and A549 cells was proportional to hydroxyl radical formation through a Fenton redox reaction of transition metals adsorbed on PM collected in Düsseldorf, Germany. The •OH-generating ability of PM and subsequent dG hydroxylation was associated with the concentration of water-soluble metals, especially Fe and V, and not with their total metal content or insoluble metal oxides. In subsequent work, significantly greater •OH generation and 8-OHdG formation in calf thymus DNA was observed for PM from urban and industrial locations in Germany than from a rural site (Shi et al., 2006). DNA strand breakage in A549 cells, preventable with hydroxyl radical scavengers, correlated with the •OH-generating capacities of the PM samples, but different slopes were observed for rural vs. urban samples. Healey et al. (2006) found evidence that the mutations induced by urban PM₁₀ in the supF forward mutation assay were derived from ROS generated by the presence of metal ions, as mutagenicity was reduced by the addition of a free radical scavenger or the metal chelator EDTA, and the types and distribution of mutations were consistent with those induced by ROS.

14.3.9 Exposure to Mixtures of Particles and Other Pollutants

“Real-world” exposure to ambient pollution involves inhalation of combinations of different kinds of chemicals, together or sequentially under some conditions. Possible interactions resulting from the inhalation of mixtures of toxicants include additive, synergistic or antagonistic effects. Interactions between different constituents of air pollution had been examined in animal studies

to only a limited degree in the literature assessed for the 1999 PM SAD. H₂SO₄ aerosol appeared to potentiate the effects of ozone, and not vice versa, so that the damaging effect of ozone in the centriacinar region of the lung was enhanced. There was also evidence that the effects of exposure to ozone or particles alone on AM physiology were attenuated by co-exposure to the two pollutants; on the other hand, particles appeared to potentiate ozone-induced neutrophilic infiltration in lung lavage. Based on the limited amount of data from animal studies, the 1999 PM SAD did not draw conclusions on the significance of combined exposure to particles and other pollutants. By the time of the US EPA 2004 PM AQCD, additional animal studies had evaluated the effects of co-exposures to particles and gases. Although some studies suggested that combined exposures resulted in enhanced responses (for example the potentiation by PM of ozone-induced proliferative changes in the epithelium of terminal bronchioles and enhanced septal cellularity in rats), the majority of studies demonstrated either no change in various health endpoints or a lack of interactive effects between PM and other substances.

In recent studies of combined exposures, Goldsmith et al. (2002) exposed OVA-sensitized mice by inhalation to CAPs (ranging daily from ~63 µg/m³ to 1569 µg/m³), or 0.3 ppm ozone, or both or neither, and analyzed effects on airway responsiveness (measured as Penh) and allergic inflammation. Exposure to CAPs alone or CAPs plus ozone produced a small increase in Penh in both normal and OVA-sensitized mice (increasing ~0.9% per 100 µg/m³ increase in CAPs). The effects of pollutant and sensitization status on airway responsiveness were additive, not synergistic, and the PM effect disappeared by 24 h post-exposure. Pollutant exposures did not alter measures of inflammation. Analysis of particle composition in relation to airway responsiveness revealed a synergistic interaction between the Al/Si particle fraction and ozone in increasing airway responsiveness in sensitized mice. The other elemental factor shown to significantly increase airway responsiveness was the S group in normal animals exposed to CAPs without ozone.

Kleinman et al. (2003) exposed aged rats (22–24 months old) nose-only to ozone alone or to low- or high-concentration mixtures of ozone with fine particles for 4 h/d, 3 d/week for 4 weeks. The particles used were EC and NH₄HSO₄ with MMADs of 0.3 µm, at concentrations of 50 µg/m³ and 70 µg/m³ in the low-concentration particle mixture and 100 µg/m³ and 140 µg/m³ in the high-concentration particle mixture, respectively. Exposure to ozone alone at 0.2 ppm did not result in significant changes to any of the measured endpoints, while exposure to the low-concentration mixture produced significant increases in endpoints such as pulmonary epithelial permeability and proliferation of interstitial cells. With the exception of macrophage Fc receptor binding, exposure to the high-concentration mixture did not produce significant effects. Exposure to particles alone was not carried out; therefore the nature of any interaction between ozone and particles could not be determined. Thomson et al. (2005) exposed rats for 4 h to particles (0–50 mg/m³ EHC-93), ozone (0–0.8 ppm) or combinations of particles and ozone and looked at effects on lung endothelin system genes. Both individual pollutants transiently increased endothelin-B receptor mRNA expression, while ozone decreased endothelin-A receptor mRNA levels. Co-exposure increased lung preproET-1 mRNA but not plasma ET-1[1-21], suggesting alternative processing or degradation of endothelins, coinciding with an increase of lung MMP-2, an enzyme that cleaves bigET-1 to ET-1. These data indicated an independent regulation of lung endothelin system gene expression by ozone and PM, but also a complex toxicological interaction with respect to plasma ET-1.

Wellenius et al. (2004) found no significant interactive effects between CAPs and CO on either arrhythmia frequency or heart rate in rats with acute MI. The responses to CO or CAPs alone were distinctly different: exposure to 35 ppm CO reduced ventricular premature beat frequency by 60.4% (p = 0.012), while exposure to a median concentration of 350.5 µg/m³ CAPs from

Boston, MA, nonsignificantly increased VPB frequency during the exposure period. None of the exposures affected heart rate. In a further study using myocardial-infarcted rats exposed for 1 h to CAPs (mean 645.7 $\mu\text{g}/\text{m}^3$), CO (35 ppm) or a combination of these pollutants, no evidence was found to support the hypothesis that short-term exposure to ambient air particles and/or CO increases the risk or frequency of supraventricular arrhythmias (Wellenius et al., 2006).

14.3.10 Summary and Considerations: Animal Toxicology

Experimental animal studies continue to explore the effects of PM on a wide range of health endpoints, and research has accelerated over recent years in many areas. The cardiovascular system has emerged as a critical target of PM toxicity. Initial evidence for particle-induced cardiovascular effects centred on ECG abnormalities, but the mechanism for cardiovascular responses was not clear at the time of the 1999 PM SAD. By the time of the US EPA 2004 PM AQCD, toxicological evidence was beginning to point to a number of hypotheses for explaining these responses, including cytokine effects on heart tissue, alterations in blood coagulability, perturbations in arrhythmogenic mechanisms, changes in endothelin levels, and involvement of neural reflexes. Recent research provides substantial evidence for the alteration of vasoactivity following exposure of animals to CAPs, urban PM_{2.5} or ROFA by inhalation or instillation. Vasoconstriction, upregulation of the endothelin system, and/or impairment of vessel dilation have been observed following both acute and chronic exposure durations. Altered vasoactivity was observed with chronic exposure to a mean PM_{2.5} concentration as low as 5 $\mu\text{g}/\text{m}^3$ in recent identified literature. The overall database, although not entirely consistent—one research group reported vasodilation in response to urban PM—suggests that vasoconstriction may be an important pathway through which PM exerts cardiovascular effects. There is also fairly consistent evidence for PM-induced thrombogenic responses, although there are questions of relevance regarding particle type and exposure route in some recent studies. Of the studies that reported significant positive effects, several used pulmonary exposure to combustion-generated or ambient particles, while several others employed an intravenous exposure route or used silica or artificial polystyrene particles. One study using relatively low levels of carbon particles found no evidence of an effect, while another with urban PM reported a reduced level of fibrinogen. Though limited, the available data generally support the hypothesis that exposure to PM may produce prothrombogenic effects.

Cardiovascular tissue damage and inflammation due to particle exposure have been observed in a small number of recent animal toxicology studies, but conclusions cannot yet be drawn on dose–response relationships and particle types that may be most important for these effects; nor can their toxicological significance be determined from the available data. Evidence for the effect of PM exposure on the progression of atherosclerosis is also limited; however, the studies by Sun et al. (2005) and Chen and Nadziejko (2005) are intriguing in that they suggest a particle-induced enhancement of atherosclerotic lesions under exposure conditions relevant to the ambient environment. Also, the Sun et al. study suggests a detrimental interaction between particle exposure and diet. Further work is required to verify these effects and demonstrate their relevance for risk assessment, which would include determining if the effects are specific to the susceptible animal models used in these studies or whether they also occur in normal healthy animals.

A more nuanced view of the mechanisms behind PM's effects on the respiratory system is taking shape. Most experimental animal studies reviewed in the 1999 PM SAD were restricted to well-defined particle species and exposure concentrations that were not environmentally relevant. Pulmonary exposure to particles was noted to elicit a number of interrelated histological and cellular disturbances. The literature available at the time focused on the influx of

neutrophils to the alveolar surface and the expansion in size of the AM population. The molecular changes behind these effects were not entirely understood. It was recognized that particles in the fine mode were more likely than larger particles to induce acute adverse effects. The US EPA 2004 PM AQCD cited studies pointing towards the association of lung injury and inflammation with pulmonary exposure to complex combustion-related PM materials, with metals among the constituents of ambient PM identified as likely contributors to these effects. Inflammatory responses were most evident at the ~200–700 $\mu\text{g}/\text{m}^3$ concentration range. The growing toxicological database on particle-induced lung injury and inflammation supports a mechanism involving phosphorylation-dependent cell signalling, with activation of the ERK/MAPK kinase pathway and NF- κ B regulatory cascade mediating the induction of cytokines such as TNF- α , MIP-2, MCP-1 and various interleukins. This molecular chain reaction leads to the immunomodulatory and inflammatory responses associated with particle exposure. Particles invoke a defensive reaction generally similar to the response of the body to pathogens: an immune reaction is elicited that involves the activation of neutrophils, macrophages and lymphocytes, which are signalled to migrate to the lung, the site of impact following inhalation. In recent identified literature, pulmonary toxicity has been observed in experimental animals following acute inhalation of PM at concentrations as low as 90 $\mu\text{g}/\text{m}^3$ for Fe particles, 180 $\mu\text{g}/\text{m}^3$ for carbon UFPs, and 262 $\mu\text{g}/\text{m}^3$ for a mean concentration of CAPs. There are fewer recent long-term inhalation studies, and lung injury and inflammatory effects in these studies have not been reported below PM concentrations of 1 mg/m^3 .

Parameters that influence toxicity continue to be characterized. Studies with CAPs and resuspended ambient PM suggest that particle toxicity can vary by day, location and season, related to specific particle constituent concentrations. Combustion-generated particles and those from the ambient environment associated with vehicles and industry tend to be more toxic than other particles, likely due to the EC/OC, organics, metals and/or other trace elements they contain. The majority of new studies support the concept that toxicity, as indicated by markers of lung injury and inflammation, increases as particle size decreases and particle surface area grows. One recent study reported that coarse particles were more toxic than fine particles, a result supported by several *in vitro* studies, substantiating the notion that in addition to particle size, chemical composition (for example the presence or absence of endotoxin) is an important determinant of particle toxicity.

In concert with *in vivo* studies on lung injury and inflammation, a growing amount of *in vitro* research using epithelial and macrophage cell lines and various particle types has continued to delineate and characterize the molecular mechanisms behind particle-induced inflammation and cell damage. *In vitro* studies examining the relative potency of PM components underscore the complexity apparent from *in vivo* studies in identifying the specific toxic constituents of ambient PM. Ambient urban particles, often consisting of complex chemical mixtures, have been found to be more toxic than simple artificial particles such as CB and TiO_2 . Fe has commonly been correlated with the bioreactivity of PM *in vitro*, which may be linked to its ability to promote the formation of reactive oxygen species. Other transition metals linked to cellular injury include V, Zn, Cu and Ni. On the other hand, studies that treated particles to alter or isolate surface components from stripped particles show differentiated effects between the stripped or treated particles and corresponding extracts, indicating the importance of not only single components but the overall matrix. The roles of individual metals in the overall toxicity of ambient PM are difficult to interpret due to evidence of interactions between them. Recent *in vitro* studies have shown that the toxicity of ambient PM can vary by season, but generalizations are not easily made across studies. While *in vivo* studies have generally found that toxicity increases as particle size decreases, *in vitro* studies have shown that coarse particles and PM_{10} are often associated with higher levels of cytokine production, possibly due to endotoxin content, while smaller size fractions are often associated with higher levels of redox activity and apoptosis.

Recent *in vitro* work provides mechanistic support for the hypothesis that particles invoke an immune/inflammatory cascade accomplished by a series of mediators: upstream activation of cell signalling pathways and transcription factors such as NF- κ B and AP-1 that control genes responsible for immune responses, and downstream expression of chemokines and other cytokines. Co-culture studies demonstrate that particle-activated macrophages may amplify the inflammatory response in epithelial cells through mediators such as TNF- α . Some *in vitro* evidence suggests that activation of proton-gated receptors and excessive calcium influx may be involved in particle-induced inflammation and cytotoxicity.

The evidence for oxidative stress as a key mechanism involved in the toxic effects of many kinds of PM is broadening. Recent work with experimental animal models shows that markers of oxidative stress are associated with tissue damage resulting from pulmonary exposure to various particle types, and that treatment with antioxidants prior to particle exposure reduces or inhibits the inflammatory response. These findings cohere with recent *in vitro* data supporting a role for ROS and RNS in mediating particle-induced cell activation and damage. Transition metals, EC/OC and PAHs have been correlated with oxidative stress in *in vitro* models. The database generally lends credence to the stratified oxidative stress model for PM toxicity put forward by Li et al. (2002). In this model, low doses of PM provoke the first tier of oxidative stress, inducing an antioxidant enzyme response meant to restore cellular redox homeostasis. At intermediate oxidative stress levels, an inflammatory response is stimulated via activation of MAPK and NF- κ B pathways. At the highest tier, cytotoxicity caused by excessive radical production and depleted antioxidant defences leads to cell death via apoptosis or necrosis. Overall, the growing database on particle-induced oxidative stress supports the hypothesis that oxidants are critical mediators of the inflammatory and cell damaging responses elicited by the inhalation of PM.

At the time of the US EPA 2004 PM AQCD, *in vivo* and *in vitro* studies had demonstrated that various types of PM could alter the immune response to antigen challenge, and that PM may act as an adjuvant. Studies pointed toward the exacerbation of allergic AHR and/or antigen-induced immune responses by ambient PM, with both metals and DEPs implicated in these effects. Many recent studies have used animal models to examine the interaction between antigens and PM exposure in the exacerbation of inflammatory and immunological components of experimentally induced allergy. A large amount of recent data support the concept that co-exposure to PM and antigen in sensitized animals aggravates airway inflammation and specific immune responses (such as increased immunoglobulin production) compared with effects caused by either particles or antigen alone. These effects have been observed with a wide variety of particle types and sizes and with different antigens, most commonly OVA but also endotoxin and birch pollen. There is now broader evidence that environmentally relevant particles such as CAPs and urban PM from different locations can produce these responses. Smaller particles appear better able to aggravate antigen-related inflammatory and immune responses compared with larger particles, in line with other studies showing greater inflammatory effects from smaller particles. Recent animal data from experimental allergy models therefore support the concept that exposure to ambient PM may exacerbate allergic asthma.

Ventilatory effects of particle exposure in animal models summarized in the 1999 PM SAD included decreased pulmonary functional status, altered particle clearance from the lungs, changes consistent with airflow obstruction, and bronchial hypersensitivity. The US EPA 2004 PM AQCD did not draw any conclusions regarding ventilatory parameters such as FVC and peak expiratory flow rate (PEFR) in animal models. Aside from two identified studies there is no substantial new information on the effects of PM on ventilatory function. As studies of traditional lung function parameters such as FVC decline, airway reactivity in response to PM exposure

continues to be explored. Airway reactivity was discussed in the 1999 PM SAD mainly in relation to the effects of acidic aerosols in increasing bronchial reactivity. Interference with normal contractile/dilatory homeostatic processes in the airways via modulation of airway receptors involved in the maintenance of airway tone was hypothesized as a mechanism. The US EPA 2004 PM AQCD stated that available evidence was suggestive but inconclusive with regard to increased airway reactivity as a possible mechanism of action for PM. Recent studies have examined some mechanistic aspects of AHR and its induction via particle exposure. Studies with urban PM_{2.5}, CAPs and ROFA appear to support the notion that metals may be important in AHR induction, and that its underlying mechanisms are at least partly divergent from those involved in the inflammatory effects of PM; overall, however, the database on this endpoint remains limited.

The 1999 PM SAD cited a number of studies using animal models of emphysema, bronchitis and viral lung infection to examine the effects of particle exposure, but did not draw conclusions with respect to susceptibility to PM. By the time of the US EPA 2004 PM AQCD, a growing number of compromised animal models were being studied and there were consistent results showing that older animals or animals with certain types of compromised health, either genetic or induced (e.g. animals infected with bacteria or viruses), were more susceptible to instilled or inhaled particles, although the increased animal-to-animal variability in these models created greater uncertainty in the interpretation of findings. Recent work continues to examine the interactions between PM exposure and host susceptibility, especially in the use of induced or genetically modified models of compromising conditions such as hypertension, hypercholesteremia, predisposition towards atherosclerosis, and diabetes. The majority of recent identified studies with SH rats did not employ healthy rats for comparison, making it difficult to determine the extent to which hypertension increases susceptibility to the inflammatory and cardiovascular effects of particles. Conversely, much of the recent research with ApoE^{-/-} mice did use normal healthy animals for comparison, in order to demonstrate that the hypercholesteremia and predisposition towards atherosclerosis exhibited by these mice make them more susceptible to the cardiovascular toxicity of PM. Observed effects include accelerated atherosclerosis, vascular inflammation, and perturbations of heart rate and heart rate variability at environmentally relevant concentrations. These results provide a measure of biological plausibility to the hypothesis that individuals with high cholesterol or atherosclerosis may be more susceptible to the chronic effects of air pollution. As for other animal disease models, only a limited amount of research has been identified for conditions such as pulmonary hypertension, diabetes and MI, and more data are required before it can be determined how PM may enhance the adverse health effects linked to these conditions.

Research on the interaction of PM with pathogenic infection has been limited in recent years, and the few available studies have used different particles, exposure routes and microorganisms. Recent studies offer mixed results with regard to particle exposure followed by infection: two studies using CAPs and ROFA found evidence for a particle-induced slowing of clearance and increased pulmonary bacterial burden, while two other studies using urban PM and CB UFPs found no effect on resistance to respiratory infection. Studies that looked at already infected animals subsequently exposed to CAPs and CB UFPs reported a worsening of infection. *In vitro* work suggests a range of possible interactions at the cellular level between particles and pathogens, including enhanced cytokine production, interference with antimicrobial defence mechanisms, and inhibition of viral replication in lung cells. The limited amount of newly available research on genetic sensitivity/resistance suggests that Toll-like receptors may be involved in mouse interstrain differences in susceptibility to PM. Recent research on age as a PM susceptibility factor, while not extensive, provides further evidence suggesting that aged animals are more susceptible to PM-induced effects on the lung and heart.

Most research at the time of the 1999 PM SAD focused on the airway as the primary target of PM. The importance of cardiovascular effects was much more greatly appreciated by the time of the US EPA 2004 PM AQCD, but research on other systems, such as the central nervous and reproductive systems, was not identified at that time. Interest in the effects of PM on systems beyond the cardiorespiratory has expanded to a certain extent. Most importantly, work with experimental animals has provided initial evidence for the effects of PM on the CNS. Neuropathologic effects include reduced dopaminergic neuron density in mice and changes in neurotransmitter levels in rats following inhalation of CAPs, and inflammatory and stress protein responses in the brains of mice following inhalation of CAPs or instillation with ultrafine CB. There is some evidence that inhaled particles may be able to distribute to the brain, though it is not known if the neuropathic effects of PM arise via direct or indirect pathways. These studies indicate that the PM-induced systemic inflammation apparent in the cardiovascular and pulmonary systems may also extend to other target systems such as the CNS, and further research will broaden our expanding of these effects.

Only three recent experimental animal studies on developmental and reproductive endpoints were identified. Although their findings are suggestive of effects of inhaled PM on lung growth in neonates and gamma-tubulin in male gonadal cells, as well as differential sensitivity of neonatal airways to PM, these studies employed metal particles or fly ash and may not be directly relevant to the ambient environment. Previous work in this area is largely nonexistent, and conclusions as to the significance of exposure to environmentally relevant PM on developmental and reproductive parameters cannot be made based on these limited findings. There also continue to be no substantial data from experimental animal studies for determining whether inhaled PM has significant adverse effects on systems beyond the cardiovascular, pulmonary, immune, and nervous systems, although there is some indication of potential for PM-induced systemic oxidative damage in organs such as the liver and kidney.

The 1999 PM SAD considered carcinogenicity as it was investigated in terms of a “particle effect” of inert particles, and concluded that the overall evidence indicated that a number of different particle types, when inhaled for long periods of time at sufficient doses, could induce lung cancer in rats (but not in mice or hamsters). The US EPA 2004 PM AQCD did not discuss the animal cancer bioassays considered by the SAD, but stated that the genotoxicity of PM found in some *in vitro* studies supported the biological plausibility of a link between long-term exposure to particles and lung cancer. The carcinogenic and mutagenic potential of PM continues to be investigated. Carcinogenicity studies using environmentally relevant particles were not identified in recent literature, while research with other particle types remains minimal. Studies by Ress et al. (2003) and Pott and Roller (2005) point to carcinogenic effects following chronic inhalation of V₂O₅ and intratracheal instillation of various granular dusts. However, these results occurred with very high exposures to non-ambient particles, and their relevance to exposures to ambient particles at environmental concentrations is not known, although the latter results are consistent with earlier findings that pulmonary exposures to a variety of particle types can induce lung tumours in rats. Other recent *in vivo* studies demonstrate that PM can cause mutagenic and related DNA-damaging effects, including heritable mutations, chromosomal aberrations, increased micronuclei frequency and DNA strand breaks. These *in vivo* findings, though few in number, concur with the mainly *in vitro* evidence base for such effects presented in the US EPA 2004 PM AQCD. The evidence for PM-associated heritable mutations in mice demonstrated by Somers et al. (2002, 2004) implies a chain of events that begins with exposure to ambient PM and ends with presumptive heritable changes caused by specific mutagenic compounds. These results warrant further *in vivo* investigation of the potentially heritable mutagenicity of ambient PM from urban and industrial areas.

Myriad *in vitro* studies continue to provide evidence for the mutagenic potential of a variety of particle types. It is difficult to directly compare the results of PM genotoxicity tests because results depend on specific laboratory protocol and test variations, details of sampling procedure, the specific particles used and other factors. However, certain trends are apparent in the literature. Studies that analyzed PM components by fractionation and extraction have generally shown that mutagenicity resides in multiple chemical components, including organic, inorganic, water-soluble and insoluble extracts, and in aromatic, acidic, polar and semipolar fractions. The DNA-damaging constituents of PM appear not to be restricted to the PAHs, nitro-PAHs and semiquinones of the organic fraction; they also include transition metals and possibly other elements of the polar and water-soluble fractions, as water-soluble metals have been shown to be important in the DNA damage caused by PM from some large urban centres. Indeed, new studies provide evidence that PM can elicit DNA damage via transition-metal-dependent oxygen radical formation. Smaller-sized particle fractions have generally been shown to be more mutagenic than larger fractions under the same study conditions. Recent *in vitro* studies suggest that winter PM samples are more mutagenic than samples from other seasons, perhaps reflecting the influence of building heating in the winter, and traffic appears to be a major source of mutagenic components of PM, although the database is not entirely consistent. Also, PM from urban areas is generally more mutagenic than artificial particles such as CB or PM from sites not impacted by traffic or industry.

Interactions between different constituents of air pollution had been examined to only a limited degree in the literature assessed for the 1999 PM SAD, with some indication of interaction between particle aerosols and ozone. Although by the time of the US EPA 2004 PM AQCD some studies suggested that combined exposures resulted in enhanced responses to PM and other substances, the majority of studies demonstrated either no change in various health endpoints or a lack of interactive effects. Experimental animal studies employing combined exposure to particles and other pollutants continue to be scant: only five such studies were identified in recent literature. Several recent studies on the effects of co-exposure to particles and ozone reported an enhancement of lung injury, additive effects on airway responsiveness, and independent regulation of lung endothelin system gene expression, with a complex toxicological interaction with respect to plasma ET-1. Research on combined exposure to particles and CO found no evidence of significant interactive effects on either arrhythmia frequency or heart rate in rats with acute MI. Recent studies on combined exposure to particles and acid aerosol were not identified. Thus the database on combined exposure to particles and other pollutants remains limited and any substantial conclusions elusive.

14.4 Controlled Human Exposure Studies

14.4.1 Introduction

Controlled human exposure studies (sometimes referred to as clinical studies) offer a complementary approach to epidemiological investigations. The advantage of this type of study is the use of a highly controlled environment to regulate exposure and measure the degree of predetermined planned outcomes of responses in a controlled setting. In addition, such experiments provide an opportunity to examine interactions with other environmental variables, such as exercise, humidity or temperature.

Controlled human exposure studies do have limitations: for example, while potentially susceptible populations may be directly studied, for ethical reasons those with more severe pre-existing disease, who are most likely to be affected by air pollutants, are often naturally excluded from these studies. For practical reasons, studies must be limited to small groups, which may not be representative of the general population. Exposure must be limited to a short duration and to concentrations of pollutants that are expected to produce mild and transient responses. Exposures are also often limited to a single pollutant or to a very restricted pollutant mix, which never replicates the complex mixture to which populations are actually exposed. (However, recent years have seen a proliferation of studies seeking to replicate and test the complex ambient particle mix through the use of particle concentrators that generate CAPs from specific locales in real time.) Furthermore, whether or not transient responses in these short-term experimental studies predict more chronic and persistent effects is unknown.

In the most recent literature, many studies used similar protocols. In general, 10–40 subjects were exposed to $\leq 200 \mu\text{g}/\text{m}^3$ of CAPs for 2 h of intermittent exercise or rest. In some studies subjects were exposed to 10–50 $\mu\text{g}/\text{m}^3$ laboratory-generated carbon UFPs or to other types of artificial particles. All subjects were adults; some were older adults. The majority of subjects were healthy, but potentially compromised or vulnerable populations were represented by subjects with asthma, COPD or angina.

14.4.2 Review of Previous Assessments

The overall conclusion of the 1999 PM SAD was that the few controlled human exposure studies available lent little support to findings from epidemiological studies. At that time, the majority of studies were conducted using artificial particles that did not reflect the complexity of ambient particles. While effects on respiratory function were not observed in healthy subjects, older adults or those with COPD, effects on airway function were observed in asthmatics, particularly children and adolescents, exposed to acidic particles. Acidic particle exposure enhanced the effects of subsequent exposure to ozone on lung function in asthmatics but not in healthy subjects. The effects on symptoms and lung function in healthy and asthmatic adults were similar after ozone or ozone + acidic particle exposures. In contrast, concurrent exposure in children had no effect on pulmonary function, but a significant effect on symptoms in allergic or asthmatic (but not healthy) children. No significant effects were observed in one study with carbon particles, although one outlier (an asthmatic) was identified. Bronchoalveolar inflammatory effects were observed after exposures of healthy subjects to DEPs. The cardiovascular effects of PM had not been studied in humans in experimental settings.

The US EPA 2004 PM AQCD reviewed the limited findings of the small number of available controlled studies in humans exposed to a variety of particle types. A narrow range of respiratory effects were observed in some small North American studies of healthy or asthmatic

adults inhaling CAPs, including mild lung/nasal inflammation or reductions in lung volume. However, these effects were not observed consistently across studies, and other endpoints—including respiratory symptoms, arterial oxygen saturation, or host defence or immune parameters in BAL or blood—were not significantly affected. With respect to other particle types, while inhalation of iron oxide particles did not affect lung function in one study, their instillation caused transient inflammation (apparently caused by soluble iron) in another study. Additional support for a role for soluble metals in PM-related pulmonary toxicity was provided by a study in which intrabronchial instillation of aqueous extracts of particles from an operating steel mill produced greater pulmonary inflammation and injury in adults than extracts from particles collected when the mill was closed. For acidic particles, the US EPA concluded that there was little evidence linking direct acute or chronic exposure to aqueous acid aerosols to acute respiratory effects, except at levels much greater than ambient. Overall, the findings reviewed at that time provided suggestive but not entirely consistent evidence of respiratory inflammation and injury from pulmonary exposure to several types of relevant particles.

With respect to cardiovascular effects, the US EPA reported that inhalation of CAPs increased blood fibrinogen (suggestive of increased PM-related thrombotic risks) in healthy adults in two controlled studies, but not in healthy or asthmatic adults in a third study. In these studies, findings for other factors related to blood coagulation control were for the most part not affected by CAP exposure, and there was conflicting evidence of effects on cardiac function as indicated by heart rate, HRV, or ECG markers. The US EPA concluded that available controlled human exposure studies provided only very limited evidence of PM-related effects on cardiovascular-related endpoints. Further, they noted that, although some of the reported changes have been used as clinical “markers” for cardiovascular diseases, the causal relationship between such PM-related changes and potentially life-threatening alterations in cardiovascular diseases remained to be better established.

14.4.3 Respiratory Effects

Several newer studies have investigated respiratory endpoints in healthy subjects and subjects with asthma or COPD. Two studies (Gong et al., 2004, 2005) investigated the effects of exposure to CAPs (predominantly in the fine, or less than 2.5 µm, range) from Los Angeles, CA, in healthy subjects and subjects with COPD. In the earlier study, 6 healthy older adults and 13 older adults with COPD were exposed to 200 µg/m³ CAPs for 2 h with intermittent exercise; no changes in lung function or respiratory symptoms were observed. Overall, declines in SpO₂ (arterial oxygen saturation as determined by pulse oximetry) were deeper after exposure to CAPs, when compared with filtered air exposure. (Oxygen saturation may be reduced in patients with lung disease or other medical conditions.) The magnitude of this change was greater and more consistent among healthy subjects than among subjects with COPD. Unexpectedly, increasing total mass concentration was associated with smaller declines in SpO₂ immediately after exposure in all subjects pooled, but not in subjects with COPD (Gong et al., 2004).

In the second study, healthy older subjects (n = 6) and subjects of a similar age with COPD (n = 13) were exposed to 200 µg/m³ CAPs for 2 h while exercising intermittently. No declines in FVC, FEV₁ or increases in symptoms were observed. Declines in maximal mid-expiratory flow rate (MMEF) were greater in healthy subjects than in those with COPD after exposure to CAPs. Similarly, declines in SpO₂ observed after exposure to CAPs were deeper in healthy subjects than in subjects with COPD. Subjects in this study were also exposure to 200 µg/m³ CAPs + 0.4 ppm NO₂. The effects observed after this exposure were similar to those of CAPs only, suggesting that effects were primarily driven by exposure to PM. When effects were regressed

on concentrations of components of the exposure mixture, declines in FVC and FEV₁ were significantly associated with increasing sulphate concentrations in all subjects and in subjects with COPD exposed to CAPs + NO₂. In all subjects, increasing concentrations of Fe in the CAP + NO₂ exposure were associated with smaller total symptom scores (Gong et al., 2005).

In another study of exposure to CAPs (120 µg/m³ PM_{2.5}) from Chapel Hill, NC, no changes in lung function were observed in 30 healthy subjects exposed for 2 h while exercising intermittently (Holgate et al., 2003).

In the literature published since the cut-off date for the US EPA 2004 PM AQCD (April 2002), the first studies of UFPs in controlled human exposure studies (all 2-h exposures) have been identified. Pietropaoli et al. (2004) exposed groups of 12–16 healthy adult subjects to 10 µg/m³ UFPs (laboratory-generated EC) at rest; to 10, 25 and 50 µg/m³ UFPs with intermittent exercise; or to 50 µg/m³ UFPs with intermittent exercise. In addition, 16 asthmatic adults were exposed to 10 µg/m³ UFPs while exercising intermittently. Decreases in SpO₂ were observed in exercising healthy females after exposure to 25 µg/m³ UFPs, while increases in SpO₂ were observed in resting, healthy males exposed to 10 µg/m³ UFPs. Other effects were only observed at the highest exposure concentration. Twenty-one hours after healthy subjects were exposed to 50 µg/m³ UFPs, decreases in FEF_{25–75} and CO diffusing capacity (a measure of the lung's ability to take up non-reactive gases, which is reduced with some lung diseases) were significantly greater than after air exposure. Exposure to 50 µg/m³ UFPs also resulted in declines in tidal volume. No changes in respiratory or miscellaneous symptoms were reported in healthy subjects, and no effects were observed in asthmatic subjects, with the exception of a decline in tidal volume after CAP exposure compared with exposure to filtered air.

In a second study, no changes in symptoms or lung function were observed in groups of 12 healthy adults exposed to 10 µg/m³ laboratory-generated carbon UFPs at rest or to 10 and 25 µg/m³ UFPs while exercising intermittently; the same result was seen when 16 asthmatic subjects were exposed to 10 µg/m³ UFPs while exercising intermittently (Frampton et al., 2004).

Few effects were observed in studies of exposures to other artificial particles. No changes in respiratory symptoms were reported after 12 healthy subjects were exposed to 500 µg/m³ fine ZnO or 500 µg/m³ ultrafine ZnO for 2 h at rest (Beckett et al., 2005). After 36 healthy subjects were exposed for 3 h to 0, 500, 1000 or 5000 µg/m³ calcium carbonate (CaCO₃) (mean aerodynamic diameter 15 µm) some decreases in nasal saccharin transport time and nasal patency were observed, as well as increases in reported nasal discomfort with increasing concentration. The authors concluded that these results showed a protective response of nasal mucosa to particulate exposure (Riechelmann et al., 2003).

14.4.4 Effects on Biological Markers

Changes in biological markers, such as cell counts, clotting factors or markers of inflammation, may influence both the cardiovascular and respiratory systems, as well as resulting in systemic effects. In the most recent literature, changes in markers were reported after exposure to CAPs or high concentrations of some specific particle types but less so after exposure to laboratory-generated ultrafine carbon particles.

In studies of CAPs from Los Angeles, CA (study details presented in Section 14.4.3), exposure resulted in an increase in peripheral blood basophils 4 h after exposure in healthy subjects but not in subjects with COPD, whereas an increase at the same time point after exposure to filtered air was only observed in subjects with COPD. No changes in other cell counts (white cells, neutrophils, lymphocytes, monocytes or eosinophils) were observed. In addition, no changes in fibrinogen, factor VII, von Willebrand factor (vWf) or platelets in peripheral blood, or

alterations in white blood cells (WBCs), columnar epithelial cells, IL-6 or IL-8 in induced sputum were observed in this study (Gong et al., 2004). In a later study, the decline in percentage of columnar epithelial cells measured in sputum after exposure to CAPs, but not CAPs + NO₂, was greater in healthy subjects than subjects with COPD. No changes in percentages of monocytes, neutrophils or eosinophils were observed (Gong et al., 2005).

A reanalysis, using principal component analyses, was done of an earlier study (Ghio et al., 2000) in which 37 healthy adults from Chapel Hill, NC, were exposed to CAPs (5–30 µg/m³ PM_{2.5}) for 2 h while exercising intermittently. It identified associations between increased neutrophil inflammation and a sulphate/Fe/Se factor, as well as increased levels of fibrinogen and a Cu/Zn/V factor. The authors suggested that the components associated with neutrophil inflammation may result from sulphurous smog and photochemical air pollution and that the Cu/Zn/V factor suggested sources of various combustion processes (Huang et al., 2003c). In a similar study in healthy adult subjects, a dose-dependent increase in neutrophils (measured as percentage or absolute number) and a decrease in percentage macrophages were observed in lavage fluids, in addition to an increase in blood fibrinogen 18 h post-exposure. After observing no changes in bronchial tissues, the authors concluded that CAPs induced modest inflammation in lavage measurements that were not reflected in proximal biopsy (Holgate et al., 2003; study details provided in Section 14.4.3).

In another study (Ghio et al., 2003) 14 healthy Chapel Hill adults were exposed to CAPs (approximately 120 µg/m³ PM) for 2 h with intermittent exercise. Positive linear relationships were observed between the PM concentration and increases in fibrinogen and decreases in WBCs, as well as a weaker association with decreases in LDH 24 h post-exposure. The authors suggested that these changes are unlikely to reflect injury, but may serve as potential biomarkers of exposure. Exposure to CAPs did not result in changes to other mediators (CRP, IL-6, TNF or ET-1) or coagulation factors (D dimers, Protein C, vWf, prothrombin, factor 7, factor 9, plasminogen, tissue plasminogen activator or plasminogen activator inhibitor).

Effects of exposure to laboratory-generated carbon UFPs were investigated in three studies. In one study no consistent differences in sputum or exhaled NO parameter analyses were observed. When healthy subjects were exposed to 50 µg/m³ UFPs, decreases in NO production in the lower airways and partial pressure of NO in the alveoli were greater than after exposure to filtered air. Effects in asthmatic subjects were limited to an increase in percentage of macrophages after exposure to 10 µg/m³ UFPs. No changes were observed in other cell differential counts (lymphocytes, PMN, epithelial cells or eosinophils) or sputum inflammatory cytokine (IL-6, IL-8) concentrations (Pietropaoli et al., 2004; see Section 14.4.3 for study details). The authors concluded that exposure to carbon UFPs resulted in mild dysfunction of the small airways and impaired gas exchange, which did not appear to be related to airway inflammation.

In the second study (Frampton et al., 2004; see Section 14.4.3 for study details) few effects on inflammatory markers were observed in healthy or asthmatic subjects exposed to laboratory-generated carbon UFPs. The authors concluded that there was no sign of airway inflammation or activation of the coagulation cascade in either group. No evidence of systemic inflammation was observed in resting, healthy subjects, and only very limited effects were noted after other exposures (i.e. with exercise, or in asthmatics). Declines in soluble CD40 ligand and a dose-dependent pattern of smaller increases in IL-6 (males only) compared with baseline were observed after exposures of healthy, exercising subjects. Overall, no evidence was found of increases in blood cytokines or soluble adhesion molecules after asthmatic subjects were exposed to UFPs, although a decline in soluble E-selectin (adhesion molecule on vascular endothelium) compared with filtered air exposure was observed, and plasma concentrations of NO₂/NO₃ (a marker of systemic inflammation) were greater after exposure to UFPs than to

filtered air. The authors reported that observed changes in blood leukocytes and adhesion molecule expression (see below) may indicate effects on endothelial function. In exercising, healthy females, declines in monocytes and basophils and increases in CD25+ T cells were observed when compared with baseline. After exposure of asthmatic subjects, declines in basophils and eosinophils were observed immediately and at 3.5 h post-exposure compared with filtered air exposure; decreased CD4+ T cells were also noted.

Frampton et al. (2006) reported on the effects of UFP exposure on blood leukocyte expression of adhesion molecules (an indirect indication of pulmonary vascular endothelial function). The results from all but one exposure (16 healthy adults exposed to 50 µg/m³ UFPs) were reported in detail in Frampton et al. (2004). Exposure of healthy subjects to 10–25 µg/m³ UFPs with intermittent exercise resulted in concentration-related declines in monocyte expression of CD54 (ICAM-1) but no clear concentration-related changes in CD62L (L-selectin). Declines in expression of CD49d, and CD23, CD32 and CD64 (low affinity receptors for IgG) on PMNs, as well as a decline in monocyte expression of CD49d (females only), were also reported in Frampton et al. (2004). In healthy subjects exposed to 50 µg/m³ UFPs with intermittent exercise, PMN expression of CD18 (part of adhesion molecule complexed with CD11a or CD11b) declined but expression of CD11a (part of LFA-1) increased. Declines in monocyte expression of CD54 were greater in males than females, while increased expression of CD18 was less than observed after exposure to filtered air. After asthmatics were exposed to UFPs with intermittent exercise, expression of CD11b on monocytes and eosinophils declined, as did expression of CD54 on PMNs, but expression of CD62L on PMNs increased in males. In addition, Frampton et al. (2004) reported decreased expression of CD16 on PMNs but increased expression on lymphocytes. The authors concluded that there was no convincing evidence of a consistent biological response or of gender differences after exposure of resting, healthy subjects to 10 µg/m³ UFPs, although in females blood monocytes showed a small increase in expression of CD54 (ICAM-1), and lymphocytes showed a small increase in expression of CD49d (part of VLA-4 adhesion molecule) and CD11b (part of Mac-1 adhesion molecule) (Frampton et al., 2004). Overall, the authors suggested that the changes associated with carbon UFPs may be consistent with a pattern of retaining leukocytes in the pulmonary vasculature.

Studies of the effects associated with exposures to other pollutant mixtures have been limited. Exposure of 30 healthy subjects for 3 h to high concentrations of urban dust samples (150 or 500 µg/m³ by a nose-only exposure system) resulted in increases in IL-1B, IL-6 and IL-8 measured in nasal secretions (Riechelmann et al., 2004). In healthy adult subjects (n = 12) the only difference observed between instillation of 100 µg/PM_{2.5} from industrial and non-industrial areas was an increase in percentage of monocytes recruited into alveolar spaces, as measured in BAL 24 h post-exposure in the first group. Compared with saline exposure, increases in percentage of monocytes recruited to alveolar spaces, lower granularity and autofluorescence of monocytes, and increases in IL-6 and TNF-α were observed after instillation of ambient PM_{2.5} from an industrial area, but not from a non-industrial area. No changes in other markers (IL-8, IL-1, total protein, albumin or LDH) were observed (Schaumann et al., 2004). In two other studies, no evidence for inflammation or effects on coagulatory markers was reported. After 12 healthy older adults and 20 older adults with angina were exposed to 50 µg/m³ carbon particles, 200 ppb SO₂ or carbon particles + SO₂ for 1 h at rest, no evidence for systemic inflammation or coagulation (blood counts, platelet aggregation or CRP) was reported (Routledge et al., 2006). Similarly, no effects on differential cell counts in blood or induced sputum, on blood cell surface markers, or on circulating coagulation factors or cytokines were observed in healthy subjects exposed to ultrafine or fine ZnO (Beckett et al., 2005; study details described in Section 14.4.3).

14.4.5 Cardiovascular Effects

Like previous assessments, recent controlled human exposure studies provided limited evidence of an effect of CAPs or laboratory-generated particles on changes in cardiovascular endpoints.

Few cardiovascular effects were reported in two studies of exposure to CAPs in Los Angeles, CA (Gong et al., 2004, 2005; study details reported in Section 14.4.3). No changes in heart rate were observed in the earlier study; however, increases in ectopic heartbeats were reported in healthy subjects, while decreases were observed in subjects with COPD. In addition, HRV over multi-hour intervals (as SDNN) was lowered by CAP exposure in healthy subjects but not in those with COPD. In the more recent study an increase in heart rate was observed after exposure to CAPs or NO₂ individually but not after co-exposure to both pollutants. Across studies there was no apparent pattern of reported changes in blood pressure, and in the first study there was no difference in the cardiovascular symptoms observed after healthy subjects and subjects with COPD were exposed to filtered air or CAPs.

Compared with a previous study that differed slightly in design, in which no effects on HRV were observed in exercising younger subjects (average age: 28.8 ± 0.9 years) exposed to an average of 105.8 ± 12.6 µg/m³ PM_{2.5} in CAPs (Ghio et al., 2000), elderly Chapel Hill subjects (n = 10) appeared more susceptible to declines in HRV induced by exposure to CAPs (40.5 ± 8.6 µg/m³ PM_{0.1-2.5}) for 2 h while resting. Decreases in HRV in the high frequency (HF) range and pNN50 were observed immediately after exposure, lasting up to 24 h post-exposure (Devlin et al., 2003). These findings are consistent with the evidence from epidemiological studies that the elderly appear more susceptible to the cardiovascular effects of PM.

Brook et al. (2002) reported the results of a study in which healthy adults exposed for 2 h to Toronto CAPs (ca. 150 µg/m³ as PM_{2.5}) with added ozone (ca. 120 ppb) had significant brachial artery vasoconstriction compared with filtered air inhalation. There were no significant effects on endothelial-dependent and –independent vasomotion determined by flow-mediated dilatation and nitroglycerin-mediated dilatation, respectively. In subsequent reports, the brachial artery vasoconstriction was significantly correlated with the OC and EC content of the ambient PM, but not with total PM or a number of trace elements and inorganic constituents (Urch et al., 2004). There was also a significant decrease in diastolic blood pressure (but not systolic blood pressure or heart rate) with CAP + ozone exposure compared with filtered air, which was significantly correlated with OC concentration but not total PM_{2.5} mass (Urch et al. 2005).

In the only study that investigated the cardiovascular effects associated with exposure to laboratory-generated carbon UFPs (details of this study are discussed in Section 14.4.3), no changes in heart rate were reported and no pattern of change in blood pressure was observed. Decreases in QT interval were observed in exercising healthy subjects and male asthmatic subjects. Increases in the standard deviation of QT interval and the standard deviation of the QT peak duration in asthmatic subjects were driven primarily by changes in female subjects. The authors concluded that no significant changes in HRV, repolarization, ST segment or heart rate were observed in healthy subjects exposed at rest. While decreasing trends in HRV parameters were observed in asthmatic subjects, they were not significant. The recovery of HF immediately after exposure to UFPs in exercising healthy subjects was less than after exposure to filtered air, but no differences were observed at 3.5 h post-exposure (Frampton et al., 2004).

Few effects were observed in studies of individual particle types. No changes in heart rate, blood pressure, HRV or ventricular repolarization in healthy adult subjects were reported after inhalation of fine or ultrafine ZnO (Beckett et al., 2005; details of this study are discussed in Section 14.4.3). After older adults were exposed to laboratory-generated particles with or without SO₂, no changes in blood pressure were observed. Compared with exposure to filtered

air, unexpected increases in HRV parameters (R-R interval, SDNN, RMSSD, low frequency (LF)) were observed immediately but not 4 h after exposure of healthy subjects to laboratory-generated carbon particles. After co-exposure to particles + SO₂, declines in measures of HRV were observed and there was evidence that effects of SO₂ on RMSSD and SDNN appeared to be modulated by exposure to carbon particles. No changes in HRV were reported after any exposure in subjects with angina. When healthy subjects and those with angina were compared, declines in RMSSD and SDNN were significantly different between the two groups (Routledge et al., 2006).

14.4.6 Summary and Considerations: Controlled Human Exposure Studies

The majority of new controlled human exposure studies have simultaneously investigated several health-related endpoints. Most recent studies were conducted using healthy subjects or were comparing healthy subjects with a group of subjects compromised by asthma or COPD. Compared with earlier studies, there has been a move away from the use of artificially derived particles towards the use of CAPs. The review period covered for this assessment includes the publication of the first of these studies investigating the effects of UFPs. The studies reviewed benefited from certain design and exposure similarities (e.g. 100–200 µg/m³ CAPs or 10–50 µg/m³ laboratory-generated UFPs for 2 h, often while exercising intermittently). Although typical ambient PM levels in Canada are generally much lower than the CAP concentrations used in the studies reviewed, occasional short-term PM_{2.5} concentrations within or even exceeding this range were reported at a number of sites across Canada during the period covered by this assessment (Environment Canada, 2006).

The most relevant of the controlled human exposure studies are those in which subjects were exposed to CAPs by inhalation, and these are emphasized in this summary, while drawing on studies with other particle types for support.

With respect to respiratory effects and associated biomarkers, the results of recent controlled studies in humans are generally consistent with those summarized in the US EPA 2004 PM AQCD. In both the earlier literature and the more recent studies reviewed in this assessment, subjects (most often healthy adults) inhaling CAPs at high but relevant concentrations exhibited mild pulmonary, systemic or nasal inflammation in a number of studies, though not in all. There were also CAPs-related reductions in lung function and SpO₂ in a small number of these studies, whereas none reported significant increases in respiratory symptoms. In the recent literature, those effects that were observed (e.g. declines in measurements of lung function or SpO₂) were greater in healthy subjects than in subjects with COPD. This contrasts with early findings from the 1999 PM SAD, in which effects on respiratory function were not observed in healthy subjects, older adults or those with COPD, but were observed in asthmatics, particularly children and adolescents, exposed to acidic particles. The most likely explanation for these contradictory results is the source and type of particles used in exposures (i.e. acidic particles vs. CAPs).

The range of respiratory effects observed in studies with less relevant particle types or routes of exposure was more limited, though inhalation of high mass concentrations of laboratory-generated UFPs was associated with reductions in lung function, SpO₂, and CO diffusing capacity in one study. In two other recent studies, inflammatory responses were observed with endobronchial instillation or nose-only exposure to ambient PM from industrial or urban areas, providing additional support to the findings reviewed in earlier assessments.

The study of potential cardiovascular effects associated with exposure to particles is relatively new. In the studies reviewed in the US EPA 2004 PM AQCD and in this assessment, there was only limited evidence from controlled exposure studies in humans of CAPs-related effects on cardiovascular endpoints. The most consistent finding was an increase in blood fibrinogen in most studies of subjects inhaling CAPs, a biochemical change suggestive of PM-related increased risk for prothrombic effects. However, this finding was not accompanied by corresponding changes in blood coagulability or in other factors related to blood coagulation control, and the causal relationship between such PM-related changes and potentially life-threatening alterations in cardiovascular diseases still remains to be established.

The evidence for effects on cardiac functioning is still more limited. Decreased HRV was reported in elderly subjects exposed to CAPs in two controlled studies, but not in young subjects in an earlier study by the same group, consistent with the evidence that the elderly may be more susceptible to the effects of PM on autonomic regulation of the heart. Increased ectopic beats were associated with CAPs exposure in one study. Combined exposure to Toronto CAPs and ozone caused constriction of the brachial artery in one study, which is intriguing in light of the findings of potential effects on endothelial function in some controlled human exposure studies with carbon UFPs. While there were reports of effects on heart rate, blood pressure, and cardiovascular symptoms in some studies, these were not consistently observed, to the extent that sometimes the changes were in opposite directions in different studies.

Although component analyses were very limited in the more recent controlled human exposure studies reviewed, the results of some studies continue to implicate transition metals, in addition to SO₄, in the toxicity of ambient PM. Following exposure to CAPs, linkages were made between Fe/Se/SO₄ and increases in neutrophils, as well as between Cu/Zn/V and increases in blood fibrinogen. Sulphate and Fe components were also associated with decrements in lung function and decreases in symptoms, respectively, after exposure to CAPs. Decreased artery diameter and diastolic blood pressure in subjects exposed to CAPs plus ozone were correlated with the OC and (for vasoconstriction only) the EC content of the ambient PM.

Previous assessments have concluded that controlled human exposure studies lent only very limited support to the findings of epidemiological studies. The evidence base has been strengthened somewhat with increasing numbers of studies of subjects exposed to CAPs, the results of which have confirmed the respiratory and cardiovascular systems as targets for PM-related toxicity, and for which some findings are fairly consistent (e.g. increases in blood fibrinogen). However, the evidence base from these studies remains limited, as a consequence of the limited number of more recent studies for any given endpoint, and the restricted and (for some endpoints) somewhat inconsistent range of significant PM-related findings. This is in contrast to the often positive effects for similar endpoints observed in panel studies and may be due to several factors. They include the use of small sample sizes in the controlled studies; the short duration of exposure in the controlled studies (2.5 h or less), compared with the continuous exposures and longer duration of the exposure metric in the panels (typically 24 h); and the relatively healthy status of the experimental subjects.

14.5 Acute Exposure Epidemiological Studies

Epidemiological studies represent a critical way to examine the possible effect of air pollution on population or community health responses. Epidemiological studies of the potential effects of ambient PM on human health explore the associations between changes in ambient levels of PM and the occurrence of particular health endpoints. Since these observed relationships are often of small magnitude and are vulnerable to confounding from factors such as seasonal cyclic variations and co-pollutants, a rigorous statistical analysis is necessary in order to detect any existing effect.

Six major epidemiological study designs can be identified that focus on either the acute or the chronic effects of airborne pollution:

- *Time-series studies*, which investigate the acute effects of PM—i.e. temporal associations between the daily variation in PM levels and daily counts of mortality, hospital admissions and emergency room visits;
- *Case-control studies*, which compare the risks of elevated exposures to PM in people with a certain disease (cases) to those without the disease (controls);
- *Case-crossover studies*, a variant of case-control studies, which compare individual health outcomes and the air pollution level at the time of the event to conditions that prevailed before and after the health problem occurrence. This type of study was conceived to evaluate the effect of transient exposure on acute events;
- *Panel studies*, which investigate the association between variation in air pollutant levels and repeated measurements of health outcomes in a defined group of subjects;
- *Cohort studies*, which explore chronic effects—i.e. the association between cumulative exposure and mortality or morbidity endpoints such as chronic diseases and lung function decrements;
- *Cross-sectional studies*, which focus on the association between current exposure and endpoints such as mortality and cardiovascular or respiratory effects. Such studies have often been applied to the examination of long-term or chronic effects in relation with air pollution, but this design can also be used to study acute effects of air pollution.

Most of the recent acute effects epidemiological studies have been time-series in nature. However, the same time-series data can be analyzed as time-series (e.g. Poisson regression) or with case-crossover methods, and more investigators have used this latest approach in the past few years. Recent studies of acute mortality and hospitalizations include investigations of both respiratory and cardiovascular endpoints.

For time-series studies, both the series of daily health outcome rates and the series of daily air pollution concentrations are subject to strong seasonal, sub-seasonal, and day-of-the-week variations as well as long-term trends. At one time, generalized additive models (GAMs) with LOESS smoothers had become the standard method to adjust for these temporal fluctuations in time-series studies. However, this technique was found to yield biased estimates of risks and standard errors if the default settings in the GAM function of the S-plus software package were used, although systematic reanalyses using more appropriate techniques indicated that the PM association persisted in the majority of studies (HEI 2003). Most researchers have subsequently employed techniques that did not suffer from this bias (e.g. generalized linear models (GLMs) with natural splines, or GAMs with stricter convergence criteria). In this review, when GAM methodology that may suffer from this bias was used, this is noted in the study account.

As much as possible, the current analysis only considers the highest risk estimates (significant or non-significant) reported in each individual study from Canada, the US, Europe and Australia. Studies from other locations that are potentially less relevant to Canada because of differences in such things as exposure levels, climate and lifestyle are discussed in less detail. Wherever relevant and possible, to allow comparisons across studies, risk estimates (risk/rate ratios as well as relative risks and 95% confidence intervals) were converted to a percentage risk increase per a standardized increment of $10 \mu\text{g}/\text{m}^3$, of a given PM size fraction, assuming a linear association between the particulate air pollutant and specific health outcomes.

14.5.1 Mortality

14.5.1.1 Summary of Previous Assessments

The 1999 PM SAD acknowledged the association between short-term exposure to PM and all-cause mortality based on the results of epidemiological studies conducted in 20 cities across North America, Latin America and Europe. For each $10 \mu\text{g}/\text{m}^3$ PM_{10} increment the estimated risk for mortality varied from 0.4% to 1.7%, with mean PM_{10} concentrations ranging from $28 \mu\text{g}/\text{m}^3$ to $115 \mu\text{g}/\text{m}^3$. The SAD highlighted the consistency of results that were obtained in various locations with different pollutant mixtures, providing strong evidence for an effect of exposure to PM on human health.

However, some major uncertainties remained, such as the effects associated with particular components of PM, and potential exposure misclassification resulting from the use of ambient air monitors as opposed to personal exposure data. The “harvesting hypothesis” (also called “mortality displacement” or “harvesting effect”) which posits that air pollution only advances, by a few days, the deaths of vulnerable persons (thus having limited public health implications), was also identified as an issue requiring further clarification.

Health Canada identified eight key areas in the mortality section of the US EPA 2004 PM AQCD. First, the mortality results (generally positive and statistically significant) were similar and of similar magnitude to that of the US EPA 1996 assessment, including positive and significant associations with $\text{PM}_{2.5}$ and PM_{10} , but inconclusive evidence for $\text{PM}_{10-2.5}$ and UFPs. However, results reported from multi-city studies revealed higher degrees of heterogeneity than studies in the earlier report. Secondly, the importance of model selection was highlighted, as demonstrated by the controversy over GAMs, which indicates the necessity of data sensitivity analyses of any chosen model. The third area was a conclusion that although other pollutants confounded the PM effect to some extent, they generally did not affect the significance of the PM risk estimates. Fourth, the role of specific components of PM was assessed in North American and Canadian studies with results suggesting PM-associated mortality may be linked to NO_2 , sulphates and coefficient of haze (COH); however, variation in effects across locations was observed. Fifth, it was reported in source apportionment studies from the US that anthropogenic pollution was an important factor in the estimated increased mortality, while results of studies on crustal materials remained negative. Sixth, some newly available studies of cause-specific mortality confirmed the effects of PM on total non-accidental mortality, with larger estimates for cardiovascular, respiratory and cardiorespiratory risk. Seventh, time lag analyses generally revealed maximum effect at 0–1 d lags, with some studies showing a second peak for 3–4 d lags. Evidence for larger effects was also reported when measurements were taken over multiple lag days. Finally, the US EPA concluded that the acute mortality studies reviewed in this assessment did not provide any substantive evidence for a threshold of effects. The existence of a threshold for PM would imply that there are concentrations below which exposure to PM does not produce adverse effects whatever the exposure duration or other environmental conditions. Such a phenomenon was investigated in examining the shape of the dose–response

curve of PM exposure in several short-term (e.g. Daniels et al., 2000) and long-term studies (Pope et al., 2002); in both cases, the analysis revealed a quasilinear association between PM exposure and mortality, with no apparent threshold. Pope (2000) provided a convincing analysis of the threshold issue and concluded that there was no evidence of a threshold for cardiopulmonary mortality related to PM exposure.

14.5.1.2 All-Cause Mortality

A substantial number of new acute mortality studies originating from North America (26), Europe and Australia (19) Asia, Latin America and Mexico (11) have been reviewed in the current assessment. These analyses were carried out in various conditions, using different approaches and statistical models. The majority of studies were time-series; 10 case-crossover studies were also reviewed.

Multiple-pollutant analyses have been conducted in 14 studies. Most studies used PM₁₀ as their PM metric (n = 40); PM_{2.5} was used in 13 studies and BS in 10 studies. Other metrics that were used included light scattering coefficient (bsp), COH, TSP and UFPs.

In order to increase the statistical power of a study, many researchers have used multi-city designs. This approach also provides other advantages, such as avoiding publication biases that can occur in single-city time-series studies. (Anderson et al. (2005) provided evidence of publication bias in studies of PM-related increases in mortality, hospital admissions, and cough symptoms.) Approximately 30 multi-city acute mortality studies were included in this assessment, including publications from the two largest projects of the last decade: the National Mortality and Morbidity Air Pollution Study (NMMAPS) in the US and the Air Pollution and Health: A European Approach (APHEA) project in Europe.

14.5.1.2.1 Canadian studies

A total of seven Canadian studies have been published during the review period. Among them was one global meta-analysis conducted by the Canadian researchers Stieb et al. (2002). They studied total daily mortality and older adult (>65 years) mortality as well as respiratory mortality from studies conducted in North and South America, Europe, Asia, Australia and New Zealand. Daily average concentrations of PM₁₀ (with a mean of 26.9 µg/m³ for Canadian data and 34.3 µg/m³ for US data), CO, NO₂ and SO₂ and daily maximum concentration of ozone were considered in this analysis. For single- and multi-pollutant model estimates, cause of death (respiratory and circulatory), age and season (warm and cool) were also used. Various methods (Shumway filter, locally weighted scatterplot smoothing (LOESS), Fourier series, spline smoothers, autoregressive techniques or dummy variables) were applied to control for temporal cycles and weather. Although unequal in strength, all studies that used methods to control for the confounding effects of weather (at least by including relative humidity or temperature as covariate) were considered acceptable. The pooled mortality excess risk estimates were calculated with fixed or random effect models when the between-study variance was greater than zero. Heterogeneity among studies was partially accounted for by differences in variability of pollutant concentrations. To assess the sources of heterogeneity in location-specific estimates, risk estimates and the standard error (SE) from individual studies were regressed against single independent variables consisting of the mean or median and the standard deviation of air pollutant concentration and mortality rate from that study. Regression against mean or median values was weighted by the inverse variance of the percentage excess mortality from that study. TSP and BS were converted to PM₁₀ concentrations by factors of 0.55 and 2.2, respectively.

In a single-pollutant model, the pooled all-cause mortality increased excess risk was 0.63% (95% CI 0.48–0.76%) per 10 µg/m³ PM₁₀ increase; in multi-pollutant models (with O₃, SO₂, NO₂

and CO), the pooled risk estimate was reduced but remained significant (0.38%, SE 0.09). Fine PM also revealed significant associations, with a 1.09% risk increase (95% CI 0.65–1.47%) per 10 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ increase in pooled estimate ($n = 18$) in the single-pollutant analysis; the multi-pollutant model result was reduced to 0.71% (95% CI 0.33–1.03%). Given the issues associated with the use of GAMs the authors published an update of this meta-analysis using only studies that did not use non-parametric GAMs (Stieb et al., 2003). They observed that a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with a smaller increase in mortality in a single-pollutant model: 0.41% (95% CI 0.25–0.6%). Using a multi-pollutant model, results were similar to the original analyses, with risk estimates reduced compared with the single-pollutant model results, but still significant at 0.32% (95% CI 0.16–0.51%). The fine PM updated risk was marginally significant, with a 0.82% increase (95% CI 0–1.63%) for an increment of 10 $\mu\text{g}/\text{m}^3$ change in $\text{PM}_{2.5}$ for the pooled estimate using single-pollutant models, but were increased in multi-pollutant models (0.87% increase (95% CI -0.65–2.35%)).

Burnett et al. (2004) conducted a multi-city study using 1981–1999 data from 12 Canadian cities to explore the effects of short-term exposure to NO_2 on daily variation in mortality; SO_2 , CO, O_3 , $\text{PM}_{2.5}$ and PM_{10} data were also collected for this analysis using a network of ambient air monitoring stations. The mean daily average values of PM_{10} and $\text{PM}_{2.5}$ across all cities were 11.4 $\mu\text{g}/\text{m}^3$ and 12.8 $\mu\text{g}/\text{m}^3$, respectively. In the main analysis, a 10 $\mu\text{g}/\text{m}^3$ PM_{10} increment was significantly associated with a 0.47% increase in total mortality in single-pollutant models; this was reduced to 0.07% after adjustment with NO_2 (a positive non-statistically significant association). A 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ (1- in 6-d sampling average of dichotomous monitors) was also associated with a positive (0.60%) but non-statistically significant increase in total non-accidental mortality, adjusted for city-specific temporal trends and weather. This study found an important effect of NO_2 that was insensitive to all PM values based on 1-in-6-d measurements. However, the researchers noted that in analyses based on daily TEOM data, which were only available from 1998 to 2000 for 11 of the 12 cities, two-pollutant models with NO_2 and $\text{PM}_{2.5}$ reduced the risk estimate for NO_2 substantially (from 0.85% to 0.32% (95% CI -0.64–1.28%) per 10 ppb), whereas the estimate for $\text{PM}_{2.5}$ was only reduced from 1.13% to 0.98% (95% CI -0.16–2.12%) per 10 $\mu\text{g}/\text{m}^3$.

Two single-city studies were conducted in Vancouver, BC. One (Vedal et al., 2003) explored the possibility of a PM_{10} threshold using TEOM data from 10 monitoring stations and found a statistically significant effect for total mortality at lag 2 d during the winter period, but not for the summer or whole year period (data not provided, graphic only), with a PM_{10} mean daily average of 14.4 $\mu\text{g}/\text{m}^3$. However, the association with PM_{10} in winter disappeared in a two-pollutant model with NO_2 . The authors concluded that their results suggested an absence of a threshold for PM_{10} . Also using data from central ambient monitors, the results from a second study (Villeneuve et al., 2003) provided some evidence for an association between an increase of 10 $\mu\text{g}/\text{m}^3$ in PM_{10} and all-cause mortality (2.39% (95% CI -0.32–5.12%) using a 3-d average (mean daily level of 19.6 $\mu\text{g}/\text{m}^3$). No statistically significant relationship between TEOM $\text{PM}_{2.5}$ and all-cause mortality was observed; however, a marginal association was noted between dichotomous $\text{PM}_{2.5}$ data and all-cause mortality (2.84% (95% CI -0.19–5.95%) per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ at lag 2 d) (mean daily level of 11.6 $\mu\text{g}/\text{m}^3$).

Other single-city Canadian studies looked at the effects of air pollution on total mortality in potentially susceptible subpopulations. A study conducted in Montreal used data from 1984–1993 and focused on the association between air pollution and mortality in older adult (≥ 65 years) individuals with diabetes, and with diabetes plus other diseases (e.g. cancer, cardiovascular or respiratory disease) (Goldberg et al., 2006). The results revealed significant associations between most pollutants and daily mortality for diabetes; a 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was associated with an 8.82% (95% CI 1.9–16.24%) increase in daily mortality from

diabetes for a 3-d mean. The same $PM_{2.5}$ increase was also associated with a 3.89% increase (95% CI 0.7–7.2%) in daily non-accidental mortality at lag 0 d among individuals classified as having diabetes before death. Significant associations were also observed, with 3-d mean lags, for individuals with diabetes and other disease(s) one year before death. The mean daily level of $PM_{2.5}$ was $17.4 \mu\text{g}/\text{m}^3$

In Hamilton, Jerrett et al. (2004) conducted a study to assess the risk of mortality associated with exposure to air pollution. Air pollutants (PM as measured by COH and SO_2) were measured using central monitors, and exposure data were divided into five zones (Downtown, Industrial North, West End, South Mountain, East End) based on proximity of an ambient air monitor. The results for the COH zonal models showed significant associations with mortality in areas with low socioeconomic conditions. In these zones (Downtown, Industrial North and the East End) the most significant 1-d lags for COH ranged from 5 to 8% increases in mortality, while multi-day excess risks ranged from 6 to 14%. In the regional models, both COH and SO_2 were significantly associated with mortality. Excess risks for an increase in the mean COH (0.42 units) for the most significant individual lags (lag 1, 2, 3 d) were identical, with a 3% increase ($p < 0.05$), while the multi-day lag effects for lags 1–3 d and 0–3 d were increases of approximately 6% ($p < 0.05$).

14.5.1.2.2 US studies

Numerous American studies were identified, several of which used the NMMAPS multi-city database, a very large data set with associated strong statistical power that permits examination of a variety of sub-issues. The original NMMAPS study was published in 2000 (Samet et al., 2000; HEI, 2000) and more recent studies have explored this database in more detail to look at issues such as GAM biases, potential population thresholds, geographical differences, confounding by season and weather, variations in sampling frequency, correlations between pollutants and the use of ambient monitors. Dominici et al. (2003) investigated the geographical aspects of the NMMAPS mortality results for the period 1987–1994 and found higher mortality risks in the eastern US and in California. Overall, this study found that a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with a 0.22% (95% posterior interval (PI) 0.1–0.38%) increase in mortality.

The same group (Dominici et al., 2005) reanalyzed the NMMAPS data to evaluate potential biases associated with GAMs when default convergence criteria were utilized. They found that the original 0.41% mortality risk estimate (posterior SE = 0.06) for PM_{10} was lowered to 0.27% per $10 \mu\text{g}/\text{m}^3$ PM_{10} when GAMs with more stringent criteria were applied and to 0.21% (posterior SE = 0.06) with GLMs using natural cubic splines, but both results remained statistically significant. This reanalysis provided evidence that multi-city studies were less affected by GAM SE underestimation than single-city analyses. In all cases, the effects of PM on mortality could not be attributed to any other pollutant. A sensitivity analysis of the smoothing functions of confounding factors (weather, temperature and humidity) for nine scenarios revealed estimates of effects ranging from 0.17% to 0.32%, with strong evidence of an association between non-accidental mortality and a $10 \mu\text{g}/\text{m}^3$ PM_{10} increment.

In a study to investigate potential population thresholds for PM-related mortality, Daniels et al. (2004) fitted three concentration–response models using PM_{10} and mortality data for 20 NMMAPS cities for 1987 to 1994. For all-cause and cardiorespiratory mortality, a natural cubic spline model showed a linear relation without indicating a threshold for relative risk, whereas for causes other than cardiorespiratory there was an apparent threshold at around $50 \mu\text{g}/\text{m}^3$ PM_{10} . For total and cardiorespiratory mortality, a log-linear model without threshold was preferred to a threshold model and to the spline model, based on Akaike’s Information Criterion.

The mortality displacement hypothesis was also studied by Dominici et al. (2003) using a subset of the NMMAPS database of daily time-series of mortality, weather, and air pollution data for

Pittsburgh, PA, Minneapolis, MN, Chicago, IL, and Seattle, WA, for the period 1987–1994. Daily mortality counts were grouped by age (<65, 65–75, and >75) and by cause of death. The method used is based on a Fourier decomposition of air pollution time-series into a set of independent exposure variables, each representing different timescales (time-domain regression method). Larger RRs of mortality were found with PM air pollution at longer time scales (14 d–2 months) than at shorter time scales (1–4 d), providing additional evidence that the association between PM air pollution and mortality does not only imply an advance in the timing of death by a few days for very frail individuals.

Roberts and Martin (2006) used NMMAPS data to evaluate a two-level Bayesian hierarchical model that was developed to overcome the sampling frequency effect, which can limit the assessment of time periods longer than a day because exposure data are only available at longer intervals (e.g. 1-in-6-d sampling). Results from this new model revealed that a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} was significantly associated with a 0.12% (SE 0.037) increase in total mortality. Zeka and Schwartz (2004) used a three-step Schwartz and Coull hierarchical model to reduce potential misclassification error associated with the use of ambient air monitor measurements and with high correlation between air pollutants (PM_{10} , SO_2 , NO_2 , CO and O_3). Results indicated that a 10 $\mu\text{g}/\text{m}^3$ PM_{10} increment was associated with a slightly greater risk than estimated by Dominici et al. (2005), at a 0.24% (95% CI 0.05–0.42%) increase in total daily mortality.

Issues related to seasonality were explored in other analyses of the NMMAPS database. The potential for seasonal variation to influence the effects of air pollution on mortality was studied using NMMAPS data from 1987 to 2000 with Bayesian semi-parametric hierarchical models, with a median daily PM_{10} concentration of 27.1 $\mu\text{g}/\text{m}^3$ (Peng et al., 2005). A statistically significant association was found for mortality in an all-season analysis (0.19% increase (95% PI 0.10–0.28%) at lag 1 d per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10}). This association remained significant in the summer at lag 1 d (0.36% (95% PI 0.11–0.61%) using data from 100 cities. However, in two-pollutant models the summer period non-statistically significant PM_{10} risk estimate calculated using 45 cities (with O_3 , NO_2 , PM_{10} and SO_2 data available) became reduced after including O_3 ; this estimate increased with SO_2 and even became statistically significant when combined with NO_2 . In another study Welty and Zeger (2005) explored the ability of time-series to adequately control for the potential confounding effect of seasonality and weather. Results indicated that weather and season were not contributing to an artificial association between PM_{10} and mortality; an increase of 10 $\mu\text{g}/\text{m}^3$ in PM_{10} at lag 1 d was associated with a statistically significant 0.2% increased mortality risk on a national scale.

Many other American studies have been conducted using different sources of data. Ostro et al. (2006) conducted a time-series analysis of data from nine heavily populated California counties to assess the risk of mortality associated with regional $\text{PM}_{2.5}$ from central monitors (mean daily averages across cities ranged from 14 $\mu\text{g}/\text{m}^3$ to 29 $\mu\text{g}/\text{m}^3$). Age, gender, ethnic group and location of death were among aspects that were assessed. A 10 $\mu\text{g}/\text{m}^3$ increment of $\text{PM}_{2.5}$ was associated with a 0.6% (95% CI 0.2–1.0%) increase in all-cause mortality using a 2-d average exposure (0–1 d lags) in all counties pooled. Statistically significant associations were also reported for older adults (>65 years) with a 0.7% increase (95% CI 0.2–1.1%) among whites, females and diabetics, as well as for out-of-hospital mortality. For the same lag (lag 2 d), all-cause mortality risks ranged from -0.3% (95% CI -1.5–0.9%) in Kern County to 2.3% (95% CI 1.0–3.6%) in Orange County. In multi-pollutant models, the effect of $\text{PM}_{2.5}$ was reduced after inclusion of CO and NO_2 (which were highly correlated with PM), but not ozone; moreover, mortality in the older adults was not affected by inclusion of any gaseous pollutant.

Fuentes et al. (2006) used the best available spatial PM data to investigate the hypothesized increase rate of mortality across the US while accounting for confounders (meteorological and

socioeconomic factors). The study period was June 2000 (one month's duration); PM concentrations were provided by two sampling stations networks with every day, every third day and every sixth day sampling analyzed, and data were modelled using a generalized Poisson regression Bayesian hierarchical model. The mean average PM₁₀ and PM_{2.5} concentrations for the month of June were 3.01 µg/m³ and 6.6 µg/m³, respectively. The highest expected mortality rates were found in the eastern states and in Southern California. On average, a 10 µg/m³ increase in PM_{2.5} was associated with a 6.6% (SD = 0.76%) increase in total mortality. The PM₁₀-associated risk was about half that of PM_{2.5} at 3.01% (SD = 0.42%) except in Texas, where coarse PM exhibited very high values.

Several case-crossover studies were also carried out in the US. Schwartz (2004a) used 1986–1993 data from 14 cities to evaluate the case-crossover design as an alternative to the non-parametric smoothing approach used to control for season and weather. Daily PM₁₀ values were sampled in order to avoid problems related to 6-d sampling methods. Correlations among a given county's monitors were calculated, excluding monitors across all counties within the lowest 10th percentile of correlations. Day of death pollution data were matched with pollution data 7–15 d before and after death, with the median average PM₁₀ across cities ranging from 23 µg/m³ to 33 µg/m³. A 10 µg/m³ PM₁₀ increment was associated with an increase of 0.36% (95% CI 0.22–0.50%) in mortality from internal causes; combining all strata (matching control days on temperature or changing sampling method for control days) had little impact on this value (0.33% (95% CI 0.19–0.46%)). A sensitivity analysis revealed that matching for temperature had little impact on the previous effect estimate, with slightly larger values than the one obtained without matching. The shape of the concentration–response relation was examined by plotting the percentage increase in deaths (relative to reference days of PM₁₀ <15 µg/m³) for ranges of particulate concentrations of 15–24, 25–34, and >45 µg/m³. Results were consistent with a linear relationship between ambient concentration and mortality. Using the same data and very similar methods Schwartz (2004b) explored the potential confounding effect of gaseous co-pollutants. This research revealed a statistically significant association between PM₁₀ and mortality (0.45% (95% CI 0.12–0.79%) per 10 µg/m³ increase) and similar results when matched with ozone or SO₂ at lags 0 and 1 d (0.45% (95% CI 0.12–0.79%) and 0.81% (95% CI 0.47–1.16%), respectively).

Zeka et al. (2005) conducted a case-crossover study using data from 20 American cities for the period 1989–2000. Again, PM₁₀ data were obtained from central monitors and the algorithm described by Schwartz (2004a) was used for averaging PM data from multiple monitors, resulting in a mean daily PM₁₀ average across cities ranging from 15.9 µg/m³ to 37.5 µg/m³. This study focused on time lag and on community-specific characteristics such as prevalence of central A/C, population density, proportion of older adults and percentage of traffic-related PM. In the unconstrained distributed lag model, a 10 µg/m³ increase in PM₁₀ was associated with all-cause mortality at lag 1 d (0.33% (95% CI 0.19–0.47%)), lag 2 d (0.15% (95% CI 0.03–0.27%)) and with a 3-d cumulative estimate (0.45% (95% CI 0.25–0.65%)), indicating a persistence of the effect over a long period. Also, both population density and percentage of traffic-related PM were reported to modify the effect of PM₁₀.

In a later study using similar methods and identical exposure data, the same authors (Zeka et al. 2006a) examined the effect of individual modifying factors such as gender, education level (a proxy for socioeconomic status (SES)), location of death, season and other health-contributing causes on PM-associated mortality. The results revealed that a 10 µg/m³ increase in PM₁₀ was associated with a 0.42% increase in all-cause mortality (95% CI 0.26–0.58%) for average PM concentrations 1 and 2 d before the event. A 10 µg/m³ increase in PM₁₀ was also associated with a 0.25% (95% CI 0.01–0.49%) increase in risk for all-cause mortality in subjects <65 years old compared with a 0.64% increase (95% CI 0.44–0.84%) in the >75 age group. Secondary

stroke diagnosis as a contributing cause was significantly associated with a 0.85% (95% CI 0.30–1.40%) all-cause mortality risk increase compared with an increase of 0.32% (95% CI 0.14–0.50%) in the absence of secondary stroke ($\alpha = 0.10$). The presence of pneumonia also increased the PM₁₀ effect on total non-accidental, stroke and MI mortality. No evidence was found for a difference in all-cause mortality by gender or race. Both lower education (less than 8 years of schooling), and medium education (8–12 school years) were associated with a non-significant increase in mortality compared with a high education level (13 years or more). Moreover, a significant difference was found by location of death, which was more than 3 times higher for out-of-hospital deaths. Finally, the examination of seasonal effects revealed that transition seasons (i.e. spring and fall) were associated with higher all-cause mortality; however, this effect was not statistically significant.

Another case-crossover study conducted in 27 major American communities explored the strength of association between PM and mortality (total non-accidental, respiratory, cardiovascular and stroke) between 1997 and 2002, and various influencing factors (Franklin et al., 2007). Communities were selected on the basis of availability of daily PM_{2.5} measurements from fixed monitors. In a pooled estimate analysis, a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{2.5} (mean daily average across cities ranging from 9.3 $\mu\text{g}/\text{m}^3$ to 28.5 $\mu\text{g}/\text{m}^3$) was associated with a 1.21% increase in all-cause mortality (95% CI 0.29–2.14%) at lag 1 d. When analyses were done to identify possible effect modifiers, age, gender (women > men), geographical area (eastern > western), attainment of the National Ambient Air Quality Standard (NAAQS) PM_{2.5} standard (areas below NAAQS > areas above NAAQS) and A/C prevalence (low A/C prevalence areas > high A/C prevalence areas) all revealed significant associations with all-cause mortality risk.

Other American studies were identified, including single-city studies (studies conducted across homogenous conditions). Klemm et al. (2004) investigated all-cause mortality among two Georgia counties' older adult populations in a time-series study using GLMs. Air quality was assessed using 15 air quality indicators from the Aerosol Research and Inhalation Epidemiological Study databank: PM_{2.5}, coarse PM mass, OC, EC, oxygenated hydrocarbons (OHCs), non-methane hydrocarbons (NMHCs), NO₃, SO₄, UFP count and surface area, CO, SO₂, NO₂ and O₃. Pollutant data were obtained from a single monitoring site located in downtown Atlanta, with a mean daily average PM_{2.5} concentration of 19.62 $\mu\text{g}/\text{m}^3$. Air pollutants were included in models by two methods: linearly or using cubic smoothing splines. Using the default model (monthly knots), positive and statistically significant effects were observed for a 10 $\mu\text{g}/\text{m}^3$ PM_{2.5} increase for all-cause mortality in individuals ≥ 65 years of age (5.52% risk increase, t-ratio = 2.95). The same increase in PM_{2.5} was also statistically significant in a model with quarterly knots (4.05% risk increase, t-ratio = 2.48). In another study Bateson and Schwartz (2004) used a bidirectional case-crossover design with conditional logistic regression to investigate mortality amongst the older adults in Cook County, IL, who had a history of hospitalization for heart or lung disease. The average PM₁₀ concentration of 37.6 $\mu\text{g}/\text{m}^3$ was calculated using an algorithm that accounted for the means and variances obtained from various EPA monitors. For each 10 $\mu\text{g}/\text{m}^3$ increase in PM₁₀ the risk of mortality increased 1.14% (95% CI 0.44–1.85%). Higher risks were observed for men (1.3% (95% CI 0.3–2.3%)) than for women (1.00% (95% CI 0.1–1.9%)). In addition, an increased risk was found among persons with heart and lung diseases, persons with a prior diagnosis of MI and those with diabetes.

The association between acute mortality and PM was also studied in two US counties (Moolgavkar, 2003). In Cook County, IL, daily PM₁₀ data were obtained from the US EPA Area Information Records System (AIRS) network, while in Los Angeles County, CA, sixth day PM_{2.5} and PM₁₀ data were provided by the California EPA. In single-pollutant analyses PM₁₀ was significantly associated with mortality in Cook County (median daily average of 35 $\mu\text{g}/\text{m}^3$) at lags of 0, 1 and 3 d (0.4%, 0.4% and 0.3%, respectively, per 10 $\mu\text{g}/\text{m}^3$ increase); in two-pollutant

analyses, this effect was significant at lag 0 d, after including NO₂ and CO (with a 0.5% risk increase in both cases). In Los Angeles County (median daily average of 44 µg/m³), statistically significant associations were observed at lag 2 d (0.6%) and lag 4 d (0.4%); however, in two-pollutant analyses, the PM₁₀ effects were attenuated and became non-significant. Some statistically significant associations were also reported for PM_{2.5} in Los Angeles, with a 0.7% mortality increase on the same day in a single-pollutant model and with 0.9% and 0.6% increases in two-pollutant models, with CO and SO₂ respectively.

In Spokane, WA, Slaughter et al. (2005) explored the association between mortality and various sizes of PM (PM₁, PM_{2.5}, PM₁₀, PM_{10-2.5}), and CO. Hourly PM values were obtained from TEOMs located in a commercial/residential area, with 90% of the daily concentrations of PM_{2.5} ranging from 4.2 to 20.2 µg/m³ and of PM₁₀ ranging from 7.9 to 41.9 µg/m³. The authors detected no associations with any PM size fractions, and no clear trends were observed across increasing or decreasing lags.

Finally, an interesting study was conducted in El Paso, TX, by Staniswalis et al. (2005). Its purpose was to assess the health effect of hourly PM₁₀ increments in a city recognized as having relatively low daily PM concentrations. It was hypothesized that the use of average daily concentrations underestimates any existing association between mortality and short air pollution episodes. Different meteorological conditions and resulting higher PM₁₀ concentrations during winter evenings were believed to increase health risks at this time of day. In addition, wind speed might contribute to variations in PM toxicity, low-speed winds being associated with atmospheric inversions and trapped urban particulates, while high-speed winds would be associated with coarse desert particles potentially contaminated with Pb and As. Such situations precluded the use of average daily PM₁₀ concentrations (which ranged from 0.2 to 133.4 µg/m³) to investigate possible associations with mortality. Instead, principal component analysis (PCA) was used, with wind speed as a surrogate for PM chemical and size profile. The effect of weather and season on daily mortality was addressed using a log-linear model. Dummy variables were included in the model for population increase and day of the week; the baseline model was equivalent to a cubic smoothing spline for time. Average dew point and temperature, cold days, humid days and hot and humid days were also considered in the model for up to 3-d lag. In a regression analysis with PM₁₀ PCA scores at lag 3 (model I), a 34 µg/m³ hourly increase in PM₁₀ (equivalent to a 10 µg/m³ PM₁₀ daily increase) in the evening peak value was associated with an average 2.06% daily mortality increase (p = 0.04). In model III (Poisson regression and daily PM₁₀), the same increase in a PM₁₀ daily average was not significantly associated with mortality (1.7%, p = 0.10). In model II (transformed PCA I (PC1) scores), a 10 µg/m³ increase in PM₁₀ was associated with an increase in mortality from 0.36 to 15% 3 d later under low and moderate wind speed conditions at the maximum and minimum values of the PC1 scores, respectively. The same range of PC1 scores resulted in only a 0.076–3.01% increase in mortality 3 d later in high-wind-speed conditions. This study revealed a statistically significant association between hourly measurements of PM and daily mortality; such an association would otherwise have been masked when using daily measurements of PM from multiple monitors. The authors of the study suggested that pooling information from multi-city monitors should be done only if the PCA results agree.

14.5.1.2.3 European studies

Several multi-city studies investigating the association between air pollution and acute mortality in Europe were identified for the period 2002–2006. Among them were several publications from the APHEA study. APHEA was a 1991–1995 project that focused on network air pollution data from 15 cities; this project was followed by a second, APHEA-2, which included 30 cities. A 5-year time-series study explored the effects of air pollution on mortality in 28 cities (Aga et al., 2003). In a fixed effects model, an increment of 10 µg/m³ daily PM₁₀ was associated with,

respectively, 0.71% (95% CI 0.60–0.83%) and 0.79% (95% CI 0.66–0.92%) mortality increases in all subjects and in individuals >65 years. Average daily concentrations of PM₁₀ ranged from 15 to 66 µg/m³. Importantly, larger NO₂ long-term average concentrations were associated with larger PM effects. A warm and dry climate also provided a larger PM estimate, which could be attributable to higher exposure to outdoor PM; moreover, cities with higher proportions of older adults had higher PM effects. BS was associated with mortality in the older adults (0.6% (95% CI 0.5–0.8%)) and in the all-age group (0.5% (95% CI 0.4–0.6%)).

Touloumi et al. (2005) investigated the possible confounding effect of influenza epidemics on air pollution (PM₁₀, BS and NO₂) effects in seven APHEA cities (median daily average PM₁₀ concentrations ranged from 13.7 to 40.2 µg/m³ across cities). After controlling for influenza epidemics by various methods, a 10 µg/m³ PM₁₀ increment was associated with 0.45% (95% CI 0.26–0.69%) to 0.67% (95% CI 0.46–0.89%) increases in daily mortality for lag 0 to 1 d. None of the methods used suggested a significant confounding effect of influenza epidemics on pollution-associated mortality.

In an earlier study by the same research team (Touloumi et al., 2004) PM₁₀ and NO₂ data from 20 European APHEA cities were used (median daily average 40 µg/m³). Single-pollutant models revealed a 0.71% (95% CI 0.60–0.83%) and a 0.67% (95% CI 0.50–0.90%) mortality increase per 10 µg/m³ increase in PM₁₀ under the fixed and random effects models, respectively. In two-pollutant models after adjusting for NO₂, a 10 µg/m³ increase in 24-h PM₁₀ was associated with a 0.42% increase in the daily total number of deaths (95% CI 0.28–0.54%) in a fixed effects multivariate model. In the fixed effects univariate model, the same PM₁₀ increase was associated with a 0.41% (95% CI 0.27–0.55) mortality increase. Since NO₂ is a recognized confounder of the PM₁₀-mortality association, tests were done to assess whether the long-term concentration of NO₂ was an effect modifier after daily NO₂ had been controlled for. The results of this analysis suggested even smaller effect estimates. The adjusted mortality estimates associated with an increment of 10 µg/m³ PM₁₀ were 0.11% (95% CI 0.03–0.20%) and 0.15% (95% CI 0.07–0.23%) for each 10 µg/m³ of average long-term NO₂ in the fixed effects univariate models and the fixed effects multivariate model, respectively. The authors concluded that the association between PM₁₀ and mortality was independent of NO₂ concentrations (an indicator of pollution from traffic), but that NO₂ still acted as an effect modifier after its confounding effect has been controlled for, suggesting a higher toxicity in particles originating from traffic.

Samoli et al. (2005) examined the shape of the concentration–response relation between PM₁₀ and mortality in 22 APHEA cities, as well as BS in 15 of the cities. Penalized regression spline models were developed for each city, and then combined into overall concentration–response curves for both PM₁₀ and for BS. These curves were roughly linear in shape for total and cardiovascular mortality, though the curves for respiratory mortality were sublinear at lower concentrations. Based on Akaike's Information Criterion, linear models fit the data much better than threshold models and slightly better than spline models. There was considerable heterogeneity in the shape of the exposure–response curves across cities, which the authors ascribed in part to differences in the air pollution mix, the climate, and the health of the populations.

The APHEA database has been used to investigate the hypothesis of mortality displacement. Zanobetti et al. (2002) examined the possibility of mortality displacement in 10 major cities from 1990 to 1997 (mean daily city averages ranged from 15.5 to 76.2 µg/m³). Results showed that apart from Rome, the estimated effect of PM₁₀ more than doubled for exposure periods up to 40 days before death, compared with 0–1 d lag results. The overall daily mortality effect of a 10 µg/m³ increase in PM₁₀ for the 10 cities was 1.61% (95% CI 1.02–2.20%) for 40 d lag, whereas at lag 0–1 d the association was 0.7% (95% CI 0.43–0.97%). Such results suggest that assessments of risk that consider short-term lag associations underestimate the number of

deaths that are advanced because of PM exposure. These results provided no evidence to support the mortality displacement hypothesis, instead suggesting that the effects associated with exposure to PM persisted much longer than a few days (up to more than a month).

Other European multi-city acute mortality studies have been conducted in France, Spain and Italy. In France, data from nine major cities were analyzed with GAMs and a combined analysis was carried out to obtain an all-cities risk estimate (Eilstein et al., 2004). The models controlled for maximal and minimal temperature, average humidity, influenza epidemics and pollen, with risk estimates for 0–1 d and 0–5 d lags. Both PM₁₀ and BS were significantly associated with a 0.8% increase in mortality for lag 0–1 d and with, respectively, 1.0% and 1.2% increases in mortality for lag 0–5 d (no 95% CI provided).

In Spain, Ballester et al. (2002) assessed the short-term effects of exposure to air pollution on total non-accidental mortality in 13 cities with varying degrees of environmental and sociodemographic conditions. Pollutant data were obtained from a local network, with mean city averages ranging from 37.8 µg/m³ to 45.1 µg/m³. Among the results, for lag 0–1 d, total non-accidental mortality was associated with 10 µg/m³ increases in 24-h mean BS (0.8% (95% CI 0.4–1.1%) in a random effects model and with PM₁₀ (0.5% (95% CI 0.1–1.0%) in a fixed effects model. In two-pollutant analyses with the same lag structure, BS was associated with mortality in both random effects models (0.8% increase (95% CI 0.3–1.3%) and fixed effects models (0.7% increase (95% CI 0.4–1.1%). PM₁₀ was also associated with a 1.3% increase (95% CI 0.6–2%) in mortality in a fixed effects model.

In Italy, Biggeri et al. (2005) conducted a time-series study in eight cities from 1990 to 1999. Ambient data were collected from a monitoring network, with the exclusion of traffic-influenced stations (mean daily city averages ranged from 36.5 µg/m³ to 77.6 µg/m³). Influenza epidemics were controlled for and temperature was modelled on two linear terms constrained at 21°C, taking into account the lagged effect of temperature. Results showed that all pollutants (SO₂, NO₂, CO, PM₁₀ and O₃) were positively and significantly associated with mortality. The overall estimate for total non-accidental mortality at lag 0–1 d associated with a 10 µg/m³ PM₁₀ increment was 0.98% (95% CI 0.35–1.61%) in a random effects model, and 0.97% (95% CI 0.27–1.69%) using a Bayesian approach. The effect of PM₁₀ was more evident in the warm season (2.53% (95% CI 1.30–3.85%)) than in the cold season (0.54% (95% CI -0.21–1.35%)). A north/south risk gradient was observed for mortality in both the first-stage model and the Bayesian city-specific model. The older adults were at higher risk for mortality in individual analyses for each pollutant; for PM₁₀, the more complex model predicted a 0.55% increase (95% CI -0.51–1.74%) for those <65 years and 1.06% increase (95% CI 0.21–1.95%) for the older adults.

Many European single-city studies were also identified. Filleul et al. (2003) conducted a study in Bordeaux, France, that focused on mortality in older adults. Air pollution data were obtained from four ambient air monitoring stations, which represented background inner city air pollution levels, with the exclusion of industry or road traffic stations (mean 24-h average of BS was 16.96 µg/m³). A 10 µg/m³ increase in BS was associated with a 1.5% (95% CI 0.3–2.8%) increase in mortality at lag 0 d. Older adult women had a greater risk on days with high pollution levels (30.1 µg/m³ mean BS) compared with low-pollution days (7.4 µg/m³ mean BS), with an OR of 5.2 (95% CI 1.32–20.65) after adjusting for smoking. The same team published results from three additional analyses. Filleul et al. (2004a) examined the effect of air pollution on short-term mortality among Bordeaux residents between 1988 and 1997 using the same air pollution station measurements. In the all-ages population, an association between an increase of 10 µg/m³ in BS and total daily mortality was observed (1.4% (95% CI 0.2–2.7%) with a 2-d mean using GAM and LOESS smoothing and 1.9% (95% CI 0.5–3.3%) using GAM and penalized spline smoothing), while a distributed 0–5 d lag model gave a 1.9% mortality increase (95% CI

0.5–3.3%) in 2-d mean with LOESS smoothing and a 1.7% increase (95% CI 0.2–3.3%) using a distributed lag model and penalized spline. Higher estimates were obtained in the older adult population, except for cardiovascular mortality. With a 2-d mean, the association between BS and total mortality was 1.9% (95% CI 0.6–3.3%) with GAM and LOESS smoothing and 2.5% (95% CI 0.9–4.2%) with GAM and penalized spline smoothing; with a 0–5 d lag, the association was 2.8% (95% CI 1.2–4.4%) in a distributed lag model using LOESS smoothing and 2.0% (95% CI 0.0–4.1%) in a distributed lag model using penalized spline.

A subsequent investigation attempted to identify characteristics that could confer higher risk in older adult individuals exposed to air pollution (Filleul et al., 2004b). Total non-accidental and cardiorespiratory mortality were investigated in a case-crossover study design and odds ratios (ORs) were calculated using conditional logistic regression models. A positive but non-statistically significant association was found between a 10 $\mu\text{g}/\text{m}^3$ increase in BS (lag 3 d) and non-accidental mortality (OR = 1.19 (95% CI 0.99–1.43)); however, many statistically significant results were observed for specific groups at lag 3 d. Each 10 $\mu\text{g}/\text{m}^3$ increment in BS was associated with an OR of 1.39 (95% CI 1.06–1.82) in single or widowed individuals, an OR of 1.30 (95% CI 1.04–1.62) in individuals not confined to the house and an OR of 1.41 (95% CI 1.05–1.90) in blue collar individuals.

Filleul et al. (2006) also carried out a study in Le Havre, France, from 1994 to 1997 to evaluate the results using background ambient air monitoring stations compared with proximate stations in air pollution time-series studies. Mortality association with BS was assessed using three scenarios: one urban, one suburban and one industrial. Background stations were not influenced by specific sources such as traffic road or industry, while proximate stations were influenced by such sources. Existing monitoring stations were then categorized as being more or less influenced by sources; i.e. they had a proportion (expressed as percentages) of influence of background or source effects. Background stations had a 0–20% influence of source effects and 100–80% influence of background effects, while balanced indicator stations had a 30–50% source effect influence and a 70–50% background effect influence. Mean daily levels of BS during the exposure period across six monitoring stations ranged from 8.53 $\mu\text{g}/\text{m}^3$ to 13.76 $\mu\text{g}/\text{m}^3$. The highest risk for total non-accidental mortality was non-significant (a 2.19% increase (95% CI -0.83–5.30%)) with 40/60% proximate-background station data weighting for 10 $\mu\text{g}/\text{m}^3$ BS. No major differences were observed between the three scenarios for any pollutant or any cause of mortality; however, the proximate stations provided larger confidence intervals. The authors concluded that in Le Havre, the use of proximate station data did not considerably modify the association between air pollution and mortality and that background stations could be used for risk assessment analysis if representative of area ambient air quality.

Also in France, Lepeule et al. (2006) reported the results of a survival analysis in a group of individuals exposed to air pollution in Bordeaux. In this design, survival times are not aggregated and the model takes into account individual factors; it also quantifies the mortality associated with exposure to air pollutants. Older adult citizens were randomly selected from a prospective cohort study of cerebral and functional factors of aging. Air pollutant data were obtained from the same four stations used in the studies led by Filleul (Filleul et al., 2004a, 2004b). Each pollutant mortality risk increase was modelled with time-dependent Cox proportional hazards, adjusting for individual risk factors such as gender, cigarette smoke and occupational exposure as well as season, day of the week, temperature, humidity and influenza epidemics. Statistically significant associations were observed between non-accidental mortality and an increase of 10 $\mu\text{g}/\text{m}^3$ in BS at lag 3 d; smokers and ex-smokers had a risk of death about of 50% (95% CI 14–97%) greater than non-smokers. Women had a lower risk of death than did men (6.1% (95% CI 4.6–7.9%)). In the distributed lag effect analysis, lag 3 d revealed a

positive non-statistically significant association for BS (12% (95% CI -1.0–0.26%)). No significant cumulative effect was reported.

In the Netherlands, Fischer et al. (2003) assessed the association between air pollution and mortality within the older adult population in an 8-year time-series study. Air pollution data (PM₁₀ and BS, NO₂, SO₂, CO, and O₃) were gathered from 16 population-oriented monitoring stations (median daily PM₁₀ concentration was 34 µg/m³). Seasonal and long-term trends, influenza epidemics, ambient temperature, relative humidity, day of the week and holidays were controlled for in the model. Positive non-significant associations between PM₁₀ and BS and total mortality were observed in subjects aged 45–64 and 65–74; a marginally significant association was observed in those ≥75 years of age, with increasing risk and narrower CI in the older age groups. A negative non-statistically significant association was also found for PM₁₀ in the <45 age group, which suggests an increased risk for total non-accidental mortality in older adult groups (no numerical data, graphics only).

In Helsinki, Finland, Penttinen et al. (2004) published the results of another 8-year time-series study. In a single-pollutant model, a significant association was reported between PM₁₀ (median daily average 21 µg/m³) and total mortality in the 64–75 age group, for lags 1 and 2 d (data not shown). In the all-age group, no consistent association was found between TSP and total mortality; however, a positive association was found between PM₁₀ and respiratory mortality. In two-pollutant models, a positive association was found between total mortality and TSP blackness at lag 1 d (a 1 × 10⁻⁵ unit increase was associated with a 2.06% (95% CI 0.09–4.06%) increase in mortality adjusted for long-term trend, humidity, temperature, weekday and influenza episodes).

In Rome, Forastiere et al. (2007) carried out a total mortality case-crossover study in residents >35 years of age to measure the influence of SES on PM-related health effects. Daily PM₁₀ values were obtained from two ambient monitors; moreover, PM, CO, NO_x and benzene values were modelled for 164 city areas based on traffic emissions. SES and income were then tabularized by traffic emission quintile and adverse chronic conditions before deaths were tabulated against SES. Four PM₁₀ categories were defined using PM emissions. Analyses revealed that a 10 µg/m³ PM₁₀ increment was strongly associated with mortality (1.1% (95% CI 0.7–1.6%)) and that higher mortality risks were reported in low income and lower SES groups than in higher income and SES groups (1.9% vs. 0.0% and 1.4% vs. 0.1%, respectively, no CI provided).

In Erfurt, Germany, Stolzel et al. (2007) carried out a time-series study to assess the role of different fractions of PM on total and cardiorespiratory mortality. Six years of air pollution data (UFPs, PM_{2.5}, PM₁₀, CO, NO, NO₂) were obtained from a representative monitoring station located 1 km from the city centre and by a major road. The mean daily levels of PM₁₀ and PM_{2.5} were 32.3 µg/m³ and 21.7 µg/m³, respectively. This study revealed some statistically significant results with UFP concentration numbers, primarily at lag 4 d. An interquartile range (IQR) increase (9748 particles) of NC 0.01–0.1 was associated with an increase of 2.9% in mortality (95% CI 0.3–5.5%) at lag 4 d; in a polynomial distributed lag model, the same increase was associated with an increase of 4.2% (95% CI 1.4–7.0%). Other positive and significant values of similar magnitude were measured with other UFP size fractions. By contrast, mass concentration (i.e. PM_{2.5} and PM₁₀) was not associated with mortality. Finally, in Serbia, Bogdanovic et al. (2006) carried out a time-series study on 2000–2003 data from Nis, using BS data from a local monitoring network. Statistically significant results were obtained for total non-accidental mortality at lag 0 d (1.13% ((95% CI 0.08–2.2%) per 10 µg/m³ increase in BS).

14.5.1.2.4 Australian studies

In the one identified study from Australia, Simpson et al. (2005) conducted a time-series analysis in four major cities (Brisbane, Melbourne, Perth and Sydney) to determine the short-term effect of PM exposure on mortality, using data from local monitoring networks. Light-scattering by nephelometry, (bsp 10^{-4} m^{-1}), PM_{10} , $\text{PM}_{2.5}$, O_3 and NO_2 were measured. Models were adjusted for daily average temperature, relative humidity, barometric pressure, day of week, holidays and influenza. All analyses included three model approaches: GAM, GLM, and GAM with penalized splines. Single-city analyses were carried out with each of the models, using a protocol based on APHEA-2. In a second stage, meta-analyses were conducted using random effects models, including tests for heterogeneity between cities. Lags 1–3 d and 0–1 d averages were considered. Single-city analysis revealed various results for total mortality; however, confidence intervals were overlapping, which revealed no significant heterogeneity. Moreover, little variation was found in the three model results, and GAM S+ results were used for further analysis. Mean 24-h PM_{10} and $\text{PM}_{2.5}$ ranged across cities ($16.30\text{--}18.20 \mu\text{g}/\text{m}^3$ and $7.5\text{--}9.3 \mu\text{g}/\text{m}^3$, respectively). A meta-analysis of the single-city estimates was also performed for each health outcome; as well, tests were carried out for heterogeneity between single-city values. In the meta-analysis of the three cities with sufficient PM data, the association with mortality was positive but not statistically significant, with a 0.2% increase (95% CI -0.8–1.2%) per $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} and a 0.9% increase (95% CI -0.7–2.5%) per $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$. However, bsp, an indicator for fine particles, revealed significant associations with total mortality in the all-age group; the highest reported risk was of 3.56% (95% CI 1.21–5.97%) per 10^{-4} m^{-1} bsp unit for lag 1 d.

14.5.1.2.5 Other studies

Eleven studies reviewed for this assessment were conducted in locations where general conditions are likely to differ from Canada environments. Most were carried out in Asia using the PM_{10} fraction, whose mean ambient levels tend to be significantly higher than what is measured in Canada. In the only multi-city study identified, Omori et al. (2003) investigated the effects of exposure to suspended particulate matter (SPM; equivalent to PM_{10}) in older adult residents of 13 Japanese cities. A significant association between SPM and mortality at lag 0–1 d was observed. Older adults were the focus of other studies. In Bangkok, Thailand, Vajanapoom et al. (2002) conducted a time-series study of mortality within several age groups, using PM_{10} with a 5-d lag average. A significant association was found in the all-age group analysis; however, when stratified by age this effect became non-statistically significant in the 55–64 age group but significant in the 65–74 and >75 age groups. Moreover, this study revealed a trend in risk with increasing age. By contrast, in Seoul, South Korea, only marginally significant results were reported in an older adult population at lag 2 d (Kim and Yang, 2005). In two studies conducted in Shanghai, China, significant relationships were observed between PM_{10} and mortality; one study used a case-crossover design (2-d moving average) (Kan and Chen, 2003a) while the other used a time-series design (lag 0 d) (Kan and Chen, 2003b). In the only other identified case-crossover design Tsai et al. (2003a) found no association between exposure to PM_{10} and mortality at lag 0–1 d in Kaoshiung, an industrial Taiwanese centre. In other time-series studies a significant association between PM_{10} and acute total mortality was observed in Seoul (Kim et al., 2004), whereas a non-significant negative association between PM_{10} and total daily mortality for a 0–2 d average was observed in Taipei, Taiwan (Yang et al., 2004a). In time-series studies of $\text{PM}_{2.5}$ no associations with mortality were observed in Chongqing, China (Venners et al., 2003) or five regions of Mexico City (O’Neil et al., 2004). Also, positive but not significant associations were observed between Asian dust storm events and daily mortality in Taipei at lag 2 d (Chen et al., 2004a) and in Seoul with a 3-d moving average (Kwon et al., 2002).

14.5.1.3 Respiratory Mortality

The adverse respiratory effects of acute exposure to air pollution have been recognized for a long time. Many of the studies that considered respiratory mortality may have also assessed total non-accidental mortality. Therefore, the section that follows will focus on the details of results for studies that have not been described earlier in this assessment, and on the results specific to respiratory endpoints for studies that have been previously described.

The current review has included a large number of respiratory acute mortality studies originating from North America (13), Europe and Australia (13) Asia and South America (12). The majority (28) were time-series studies, followed by case-crossover (6) and then other design types (2). Most studies used PM₁₀ as the PM metric. Only four studies evaluated PM_{2.5}, while BS was used in eight (all in Europe) and SPM, COH and UFP were used sparingly. Multi-pollutant analysis was used in 10 studies.

14.5.1.3.1 Canadian studies

Four Canadian studies were covered by the review period for this assessment, including a global meta-analysis led by Canadian researchers (Stieb et al., 2002) that was reanalyzed to address issues related to GAMs (Stieb et al., 2003). The latter study explored the short-term effects of exposure to PM₁₀ on respiratory mortality. In single-pollutant models, the pooled respiratory mortality excess risk was 1.32% (SE 0.9) per 10 µg/m³ increase in PM₁₀ (mean daily average was 26.9 µg/m³ for Canada and 34.3 µg/m³ for the US). When these data were reanalyzed as a result of issues surrounding the use of GAMs, the updated pooled respiratory mortality excess risk was 1.39% using non-GAM methods, and 1.2% per 10 µg/m³ increase in PM₁₀ using GAMs; both results were statistically significant (Stieb et al., 2003).

Two other Canadian studies were conducted in Vancouver, BC. First, Vedal et al. (2003) reported a significant effect of PM₁₀ on respiratory mortality for the summer period at lags 1 and 2 d. In multiple-pollutant models, the effect on respiratory mortality at lag 1 d for the summer period decreased and became non-statistically significant after inclusion of ozone (no data were provided) with a PM₁₀ mean daily average of 14.4 µg/m³. The other study (Villeneuve et al., 2003) investigated the association between daily mortality and air pollution (the mean daily level of PM_{2.5} was 19.6 µg/m³), with stratification by income. Some positive non-significant associations were observed between PM_{2.5} and respiratory mortality at lag 0 d. A 10 µg/m³ PM_{2.5} increment (using TEOM data) was associated with a 7.5% (95% CI -4.1–20.5%) increase in respiratory mortality, while the same increment (measured using dichotomous samplers) was associated with a 6.3% (95% CI -3.0–16.3%) increase in respiratory mortality. Positive associations were also observed with PM₁₀ (0.66% (95% CI -5.1–6.8%) per 10 µg/m³ at lag 0 d) and COH (3.7% (95% CI -1.7–9.3%) per 0.4 COH unit at lag 1 d). There was no evidence of an effect of SES on respiratory mortality from exposure to PM₁₀ and most other pollutants, while PM_{2.5} revealed a coherent increasing risk trend in higher income groups.

14.5.1.3.2 US studies

All nine reviewed studies from the US were multi-city in design, with most data obtained from centrally located monitors. First, a reanalysis of NMMAPS data (Dominici et al., 2003) from 88 large US metropolitan areas for the period 1987–1994 revealed a positive association at lag 1 d (0.31% (95% PI 0.15–0.5%) for cardiovascular/respiratory mortality risk per 10 µg/m³ increase in PM₁₀). The effect on combined cardiovascular/respiratory mortality was greater than that on total mortality and other-cause mortality. On a national scale, the highest risk estimates were observed in the US northeast area; temporally, the highest estimates generally occurred at lag 1 d. In this analysis, the cardiovascular/respiratory mortality pattern remained similar, with higher PM₁₀ effects in the northeast region.

In a study to investigate potential population thresholds for PM-related mortality, Daniels et al. (2004) fitted three concentration–response models using PM₁₀ and mortality data for 20 NMMAPS cities for 1987 to 1994. For all-cause and cardiorespiratory mortality, a natural cubic spline model showed a linear relation without indicating a threshold for relative risk, whereas for causes other than cardiorespiratory there was an apparent threshold at around 50 µg/m³ PM₁₀. For total and cardiorespiratory mortality, a log-linear model without threshold was preferred to a threshold model and to the spline model, based on Akaike’s Information Criterion.

Dominici et al. (2005) reported the results of a time-series study that reanalyzed NMMAPS data using information from 90 US cities. The purpose of this research was to assess the potential biases associated with the use of GAMs and default convergence criteria; for this purpose, GAMs with more stringent criteria and GLMs with natural cubic splines were used. The results indicated that the general pattern for cause-specific mortality remained the same. The highest estimate obtained using GLM was for cardiorespiratory mortality at lag 1 d (0.31% increase (posterior SE = 0.09) per 10 µg/m³ increase in PM₁₀). On a regional basis, the health risk pattern remained similar, with the highest estimates observed in the northeast, generally at lag 1 d. The pattern of cardiorespiratory mortality also remained the same, with the strongest effects of PM₁₀ observed in the northeast region. The test conducted with updated methods revealed lower heterogeneity between city-specific risk estimates; this analysis also suggested low sensitivity to different data treatment approaches.

Further analyses of the NMMAPS database were available in 2005. In a time-series study, Peng et al. (2005) explored the seasonal variation of effect of PM₁₀ on mortality in 100 US cities from 1987 to 2000 (median daily PM₁₀ of 27.1 µg/m³). Some positive results were obtained for cardiovascular and respiratory mortality, but since these estimates were similar to total non-accidental mortality, these results were not presented in the paper. Roberts and Martin (2006) also reported the results of an analysis of NMMAPS data from 109 US cities for the same period. Some more precise results were obtained from the alternative model, which extracted information on mortality for a period longer than 1 d to address sampling frequency effects. The risk estimate for cardiovascular and respiratory mortality was 0.17% (SD = 0.047) per 10 µg/m³ PM₁₀ increment.

In nine California counties Ostro et al. (2006) reported a significant positive effect on respiratory mortality for a 2-d average exposure in a time-series study (2.2% (95% CI 0.6–3.9%) per 10 µg/m³ PM_{2.5}) with daily average city concentrations ranging from 14 to 29 µg/m³. In a case-crossover study that was carried out in 27 communities in the US, significant results were also observed, with daily average city concentrations ranging from 9.3 to 28.5 µg/m³ (Franklin et al., 2007). In pooled analysis at lag 1 d, a 10 µg/m³ increase in PM_{2.5} was associated with a 1.78% (95% CI 0.20–3.36%) increase in respiratory mortality. Lower and often non-significant risks were estimated at other lags. In effect modification analyses, age was found to be statistically associated with a higher risk of respiratory mortality in individuals ≥75 years of age (1.85% (95% CI 0.27–3.44%) per 10 µg/m³ increase in PM_{2.5}) than in those <75 (1.53% (95% CI -0.67–3.75%)). Gender was also associated with risk of respiratory mortality, with risks of 1.90% (95% CI 0.14–3.65%) in men and 1.57% (95% CI -0.22–3.35%) in women for a 10 µg/m³ increase in PM_{2.5}. Community location was associated with different risk levels in the east (2.66% (95% CI 0.14–3.65%)) and the west (0.67% (95% CI -2.00–3.34%)). A higher risk was also reported for a 10 µg/m³ increase in PM_{2.5} using the previous day’s concentration in communities at or below the PM_{2.5} NAAQS of 15 µg/m³ PM_{2.5} (2.46% (95% CI -0.49–5.42%)) compared with communities above the NAAQS (1.42% (95% CI -0.22–3.35%)). Finally, as anticipated, a higher risk was found in communities having a lower prevalence (25th percentile) of A/C (2.27% (95% CI 0.27–4.27%)) compared with communities in the 75th percentile (1.04% (95% CI -1.29–3.37%)).

The effect of time lag and city-specific ($n = 20$) characteristics was the focus of a case-crossover study by Zeka et al. (2005) resulting in a mean daily PM_{10} average across cities ranging from $15.9 \mu\text{g}/\text{m}^3$ to $37.5 \mu\text{g}/\text{m}^3$. Using an unconstrained distributed lag model, a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with a 0.41% (95% CI 0.02–0.80%) increase in respiratory mortality at lag 2 d and with a 0.87% (95% CI 0.38–1.36%) increase using a 3-d cumulative estimate. For pneumonia, the same increment was associated with a 0.75% (95% CI 0.14–1.36%) increase at lag 2 d and with a 1.24% increase (95% CI 0.46–2.02%) for a 3-d cumulative estimate. Finally, using the same study design and database, Zeka et al. (2006a) investigated the effect of factors such as gender, race, education level (proxy for SES), death location and season. Among the results, the risk of respiratory mortality was increased by 0.87% (95% CI 0.38–1.36%) per $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} for a 2-d average. However, gender, race, age and education did not reveal any trend in risk level for respiratory mortality.

14.5.1.3.3 European studies

Five European multi-city studies were identified from the 2002–2006 review period.

Analitis et al. (2006) reported the results of a study on respiratory mortality conducted in 29 European centres using the APHEA database and fixed-site monitoring data (the range of median averages across cities was $9\text{--}64 \mu\text{g}/\text{m}^3$). Temperature, humidity, influenza, day of week and holidays were accounted for, as well as other unusual events. In the random effects model, increases of $10 \mu\text{g}/\text{m}^3$ (lag 0–1 d) in PM_{10} and BS were respectively associated with an increase of 0.71% (95% CI 0.22–1.20%) and 0.84% (95% CI 0.11–1.57%) in respiratory mortality. For the lag 0–5 d distributed lag model, the effects were even greater (1.24% (95% CI 0.49–1.99%) in the random effects model and 1.61% (95% CI 0.56–2.66%), also in the random effects model, for PM_{10} and BS, respectively). In two-pollutant models, the effects attributed to PM_{10} decreased with inclusion of SO_2 or NO_2 but remained unchanged with ozone; for BS, this effect also decreased with SO_2 and NO_2 but increased with ozone. Sensitivity analyses for model types indicated that decreases in effects were observed with natural splines, while use of LOESS and decreasing degrees of freedom resulted in increased estimates. An analysis of heterogeneity in city-specific effects of BS on respiratory mortality indicated greater effects in those cities with a higher age-adjusted lung cancer mortality rate and proportion of older adults.

Samoli et al. (2005) examined the shape of the concentration–response relation between PM_{10} and mortality in 22 APHEA cities, as well as between BS and mortality in 15 of the cities. Penalized regression spline models were developed for each city, and then combined into overall concentration–response curves for both PM_{10} and for BS. These curves were roughly linear in shape for total and cardiovascular mortality, though the curves for respiratory mortality were sublinear at lower concentrations. Based on Akaike’s Information Criterion, linear models fit the data much better than threshold models, and slightly better than spline models. There was considerable heterogeneity in the shape of the exposure–response curves across cities, which the authors ascribed in part to differences in the air pollution mix, the climate, and the health of the populations.

In France, Eilstein et al. (2004) conducted a time-series study of mortality in nine cities and observed significant effects on respiratory mortality (1.9% per $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} and 2.1% per $10 \mu\text{g}/\text{m}^3$ increase in BS at lag 0–5 d (no 95% confidence intervals given)). In Italy, Biggeri et al. (2005) focused on total, cardiovascular and respiratory cause mortality in eight Italian cities for the period 1990–1999. An increase of $10 \mu\text{g}/\text{m}^3$ in PM_{10} was significantly associated with respiratory mortality (lag 0–1 d) in a fixed effects model (1.74% (95% CI 0.44–3.05%)) and in the Bayesian approach (1.71% (95% CI 0.02–4.66%)). Finally, in Spain, Ballester et al. (2002) reported significant associations for PM_{10} , BS and TSP; among the

results, an excess risk of 1.3% (95% CI 0.1–2.6%) in respiratory mortality (lag 0–1 d) was found for a 10 $\mu\text{g}/\text{m}^3$ change in PM_{10} , also in a fixed effects model.

Eight European single-city studies were also identified in the review period 2002–2006. Three of these were conducted by Filleul's group in France. The first, in Bordeaux, observed a significant effect between BS and respiratory mortality in an all-ages category and in older adults (≥ 65 yrs) (Filleul et al., 2004a). In the all-ages population, the association with a 10 $\mu\text{g}/\text{m}^3$ increase in BS was 4.3% (95% CI 0.0–8.8%) for lag 0–1 d and 6.9% (95% CI 1.6–12.4%) for a 0–5 d distributed lag. Using penalized splines, these risks increased to 7.4% (95% CI 2.3–12.8%) for lag 0–1 d and 7.6% (95% CI 2.0–13.5%) for a 0–5 d distributed lag. In the older adult population, the association between BS and respiratory mortality was 3.7% (95% CI -0.8–8.4%) for lag 0–1 d and 8.2% (95% CI 2.8–13.8%) for a 0–5 d distributed lag. Again, risks increased when penalized splines were used, to 8.4% (95% CI 3.1–13.9%) at lag 0–1 d and 9.2% (95% CI 3.4–15.3%) for a 0–5 d distributed lag. The mean level of BS during the study period was approximately 17 $\mu\text{g}/\text{m}^3$.

The purpose of the second study, which was case-crossover in design, was to identify characteristics that could confer higher risk to individuals exposed to air pollution (Filleul et al., 2004b). Some statistically significant results were observed at lag 3 d. For each 10 $\mu\text{g}/\text{m}^3$ increase in BS the risk increase for cardiorespiratory mortality was 30% (95% CI 1–68%) in the total study population. Stronger effects were observed in subsets of the population: 39% (95% CI -6–107%) in women, 52% (95% CI 3–125%) in individuals >84 years, 336% (95% CI 15–1554%) in individuals with secondary school education level or higher, 62% (95% CI 7–145%) in single individuals, 42% (95% CI 3–94%) in individuals not confined to the house, 78% (95% CI 17–171%) in those with dyspnea, and 66% (95% CI 5–162%) in individuals with angina.

The third study, in Le Havre, assessed the influence of the exposure measurement location (Filleul et al., 2006). For respiratory mortality, a 10 $\mu\text{g}/\text{m}^3$ increase in BS was associated with a 4.13% increase (95% CI -6.5–15.97%) in balanced indicator station, with a 40/60% proximate–background station data weighting and with a 5.34% increase (95% CI -1.11–4.89%) for background station measurement (e.g. with 0–100% proximate–background station data weighting). In conclusion, no major differences were obtained when using proximate station data for risk assessment. In Bordeaux, Lepeule et al. (2006) reported the results of the survival analysis, observing significant associations between BS and cardiorespiratory mortality at lag 3 d with an increase of 24% (95% CI 4–47%) per 10 $\mu\text{g}/\text{m}^3$ increase in BS). The effect of smoking on cardiorespiratory death was greater than total non-accidental mortality in ex-smokers (85% increase (95% CI 18.0–189.5%) vs. 50% (95% CI 14–97%)) and current smokers (75% (95% CI -3–216%) vs. 65% (95% CI 17–132%)).

In the Netherlands, Fischer et al. (2003) estimated the association between exposure to air pollutants and daily mortality for various age groups (<45 ; 45–64; 65–74 and ≥ 75) and also examined the association with specific cause of death. After adjusting for long-term and seasonal trend, influenza, temperature and humidity, day of the week and holidays, statistically significant associations were observed between PM_{10} and pneumonia mortality in the 45–64 age group (6.95% (95% CI 0.52–13.81%)) and in the ≥ 75 group (2.94% (95% CI 1.35–4.58%)) for a 10 $\mu\text{g}/\text{m}^3$ increase. Significant associations were also reported for similar increases of BS and COPD in the 65–74 age group (20.4% (95% CI 9.5–32.4%)), and with pneumonia mortality in the ≥ 75 group (12.3% (95% CI 5.5–19.6%)). The median distribution of daily concentrations was 34 $\mu\text{g}/\text{m}^3$.

In Helsinki, Finland, Penttinen et al. (2004) conducted a time-series study to assess the relationship between air pollution and mortality. In a single-pollutant model, a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with respiratory mortality in all age groups at lag 0 d (3.94% (95% CI

0.01–7.87%)), lag 1 d (3.96% (95% CI 0.11–7.81%)) and lag 4 d (2.13% (95% CI 0.03–4.22%)) (median daily average 21 $\mu\text{g}/\text{m}^3$). In Nis, Serbia, Bogdanovic et al. (2006) conducted a time-series study that revealed an association between 10 $\mu\text{g}/\text{m}^3$ BS and respiratory disease mortality (1.73% (95% CI 0.94–4.47%)) at lag 0 d. Finally, in Erfurt, Germany, Stolzel et al. (2007) found a positive significant relationship between UFPs and cardiorespiratory mortality (3.1 (95% CI 0.3–6%) per 9748 IQR NC_{0.01–0.1}) at lag 4 d.

14.5.1.3.4 Australian studies

One Australian study considered respiratory mortality in four major cities (Simpson et al., 2005). In pooled analysis, respiratory mortality was associated at lag 1 d with a 9.48% (95% CI 1.74–17.81%) increase per 10^{-4} m^{-1} in bsp. Mean 24-h PM_{10} and $\text{PM}_{2.5}$ ranged across cities, from 16.30 to 18.20 $\mu\text{g}/\text{m}^3$ and 7.5 to 9.3 $\mu\text{g}/\text{m}^3$, respectively.

14.5.1.3.5 Other studies

Twelve studies that examined acute respiratory mortality outcome were conducted in Asia and South America, whose mean ambient levels of PM tended to be significantly higher than what is present in Canada. Asian dust storms were investigated by Chen et al. (2004a) in Taipei, Taiwan, and Kwon et al. (2002) in Seoul, South Korea. The first group found the highest increased risk for respiratory disease mortality one day after the event, while the second group reported a positive non-significant association between PM_{10} and all-age cardiorespiratory mortality.

Two studies by Kan and Chen (2003a, 2003b) looked at daily mortality in Shanghai, China. The first, a time-series study, revealed a positive non-significant association between COPD mortality and PM_{10} , while the second (a case-crossover design) reported COPD mortality risks that were similar to previous studies, with higher risks of cardiovascular and respiratory mortality than of total non-accidental mortality. In Beijing, China, Kan et al. (2005) observed a non-significant effect of PM_{10} on SARS mortality.

In Seoul, Kim and Yang (2005) found a higher respiratory mortality risk in the older adults; however, this association with PM_{10} was not statistically significant. By contrast, in Japan, Omori et al. (2003) found a significant association between exposure to SPM ($\sim\text{PM}_7$) and respiratory mortality in older adults from 13 major cities. In Bangkok, Thailand, (Vajanapoom et al., 2002) and Hong Kong (Wong et al., 2002) significant results between PM_{10} and respiratory mortality were also reported. In the latter study, there was also a significant association of PM_{10} to mortality from COPD; however, neither finding remained significant in multi-pollutant analyses with SO_2 , ozone and NO_2 (Wong et al., 2002). However, in Taipei, Yang et al. (2004a) found a non-statistically significant negative association between this size fraction and respiratory mortality, while Venners et al. (2003) found no association between $\text{PM}_{2.5}$ and acute respiratory mortality in Chongqing, China.

Finally, a time-series study by Martins et al. (2004) conducted in Sao Paulo, Brazil, focused on socioeconomic conditions and found a decreasing effect of PM_{10} on respiratory mortality with increased education and family income, and higher mortality for populations living in slums.

14.5.1.4 Cardiovascular Mortality

Cardiovascular effects resulting from acute exposure to PM have been extensively studied in recent years. During the 2002–2006 period, many toxicological studies have been carried out to assess the effects of PM on physiological processes (e.g. systemic lung inflammation, generation of ROS, cytokine production) which could explain the observed end results: changes in HRV, cardiac arrhythmia, increases in plasma viscosity, plaque rupture and thrombosis, MI, etc. The effects of exposure to air pollution on the cardiovascular system appear to imply a

complex succession of physiological and metabolic reactions that has not been fully elucidated. The following section describes the numerous recent epidemiological studies of the relationships between short-term (acute) exposure to PM and cardiovascular mortality. Since many studies that considered cardiovascular mortality also assessed total non-accidental mortality, the section that follows will focus on results and not detailed study descriptions of those studies that have been described in the previous section. Any newly introduced studies will be noted as such and will receive more attention, in order to more fully describe their parameters.

A total of 48 acute cardiovascular mortality studies originating from North America (19), Europe and Australia (15) and Asia (14) have been reviewed in the current assessment. The great majority (35) of these studies were time-series in design while only a small number of them have used a case-crossover design.

Multi-pollutant analyses were used in 13 studies, while the remainder used single-pollutant analysis. The vast majority of reviewed studies used PM₁₀ data as the PM metric; only 8 used PM_{2.5} for analysis, while BS was used in 8 studies (all in Europe) and 3 used SPM.

14.5.1.4.1 Canadian studies

Four Canadian studies are examined in the current assessment. The first (Stieb et al., 2002) is a meta-analysis of mortality studies associated with short-term PM₁₀ exposure that was reanalyzed (Stieb et al., 2003) to address methodological issues with GAMs. The mean daily average PM₁₀ concentrations were 26.9 µg/m³ in Canada and 34.3 µg/m³ in the US. However, the reanalysis did not include new estimates of circulatory mortality; therefore, the only result to report was from a single-pollutant model, in the original analysis, in which the pooled circulatory mortality excess risk was 0.7% (SE = 0.3) per 10 µg/m³ increase in PM₁₀. The other studies were single-city time-series studies, both conducted in Vancouver, BC. Over a 13-year period Villeneuve et al. (2003) observed no significant association between exposure to PM_{2.5} (mean daily level 11.6 µg/m³) and cardiovascular mortality; however, there was a significant association with TSP at lag 2 d and a marginally significant association with PM₁₀ on the same day with 3.28% (95% CI 0.0–6.63%) per 10 µg/m³ increase (mean daily level 19.6 µg/m³). In the other study, Vedal et al. (2003) found positive non-statistically significant associations between cardiovascular mortality and exposure to PM₁₀ at lags 0, 1 and 2 d during the winter but only at lag 0 d in the summer (no data shown), with a mean daily average value of 14.4 µg/m³.

14.5.1.4.2 US studies

Numerous US researchers have studied the effect of acute exposure to PM on cardiovascular mortality. The great majority of these studies used multi-city and central monitor data. Dominici et al. (2004) assessed the effects of air pollution on cardiovascular mortality in another time-series study of NMMAPS data over 7 years (1986–1993). A 10 µg/m³ increase in PM₁₀ at lag 0–1 d was associated with a 0.26% (95% PI -0.37–0.65%) increase in cardiovascular-related mortality across cities. This group also performed an analysis of data from the 88 largest US metropolitan areas for 1987–1994, which revealed a 0.31% relative rate increment for cardiorespiratory mortality (95% CI 0.15–0.5%) per 10 µg/m³ increase in PM₁₀ (Dominici et al., 2003). Similar results were found in a reanalysis of NMMAPS (Dominici et al., 2005); the cardiorespiratory mortality risk estimate was 0.31% (posterior SE = 0.09) for each 10 µg/m³ PM₁₀ increment at lag 1 d. On a regional basis, the cardiorespiratory mortality pattern remained the same, with the highest PM₁₀ effect occurring in the northeastern US and California.

Further NMMAPS analyses were conducted by other groups. In a study to investigate potential population thresholds for PM-related mortality, Daniels et al. (2004) fitted three concentration–response models using PM₁₀ and mortality data for 20 NMMAPS cities for 1987–1994. For all-

cause and cardiorespiratory mortality, a natural cubic spline model showed a linear relation without indicating a threshold for relative risk, whereas for causes other than cardiorespiratory there was an apparent threshold at around $50 \mu\text{g}/\text{m}^3$ PM_{10} . For total and cardiorespiratory mortality, a log-linear model without threshold was preferred to a threshold model and to the spline model, based on Akaike's Information Criterion. Peng et al. (2005) used NMMAPS data to assess seasonal aspects of the association between air pollution and mortality. This study provided no specific data for cardiovascular mortality, but the authors mentioned that these results were similar to those obtained for non-accidental mortality, (i.e. a statistically significant PM_{10} association with mortality at lag 1 d) (median daily PM_{10} concentration of $27.1 \mu\text{g}/\text{m}^3$). In another NMMAPS analysis, Roberts and Martin (2006) found a statistically significant association between a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} and respiratory and cardiovascular mortality (0.17% (SD = 0.047)) using a 3-d moving average model. In the same year, Ostro and collaborators published the results of research conducted in nine California counties (daily averages ranged from 14 to $29 \mu\text{g}/\text{m}^3$ across cities). (Ostro et al., 2006). A marginally significant increase in cardiovascular mortality was observed for a lag 0–1 d average exposure (0.6% (95% CI 0.0–1.1%) per $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$).

Another time-series study of cardiovascular mortality was conducted in seven North Carolina counties (Holloman et al., 2004) using a Bayesian approach as an alternate approach to Poisson GAM. The mean daily average $\text{PM}_{2.5}$ levels were $9.69 \mu\text{g}/\text{m}^3$. A $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ exposure (rather than ambient concentrations; estimated using a population exposure model) was associated with an 11.4% (95% CI 2.8–19.8%) increase in cardiovascular mortality at lag 2 d. Positive but non-significant results were also observed at lag 0 and lag 1 d; moreover, a non-significant negative result was observed at lag 3 d. When the effects of changes in ambient levels of $\text{PM}_{2.5}$ on cardiovascular mortality were considered, a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was associated with 0.09%, 0.2% and 1.0% increases and with a 1.4% decrease in the risks for cardiovascular mortality at lags 0, 1, 2 and 3 d, respectively. $\text{PM}_{2.5}$ was also associated with maximum daily temperature and inversely associated with daily average wind speed. Analyses using alternative models provided evidence that the three-stage Bayesian hierarchical model chosen for the main analysis was robust and gave results similar to those of simplified Bayesian models and classical Poisson GAMs. Finally, Fuentes et al. (2006) found a 6.0% increase in risk for cardiovascular mortality per $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ increase (mean daily level was $6.6 \mu\text{g}/\text{m}^3$) in the eastern part of the US in a monthly spatial analysis.

Franklin et al. (2007) undertook a study whose purpose was to assess the health effects of $\text{PM}_{2.5}$ in a large population-based (27 communities) case-crossover study (mean daily average $\text{PM}_{2.5}$ across cities ranged from $9.3 \mu\text{g}/\text{m}^3$ to $28.5 \mu\text{g}/\text{m}^3$). Many significant findings were observed. In pooled estimate analyses, at lag 1 d an increase of $10 \mu\text{g}/\text{m}^3$ in $\text{PM}_{2.5}$ was associated with, respectively, 0.94% (95% CI -0.14–2.02%) and 1.03% (95% CI 0.02–2.045%) increases in cardiovascular and stroke mortality. In effect modification analyses, age, gender, geographic location and A/C use were found to influence the associations between a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ and mortality outcomes. At lag 1 d, age was found to be associated with a 1.29% (95% CI 0.15–2.42%) increase in cardiovascular mortality in the ≥ 75 age group compared with 0.26% (95% CI -1.04–1.56%) in the < 75 group, and with a 1.52% (95% CI 0.37–2.67%) increase in stroke mortality in the ≥ 75 group, compared with -0.78% (95% CI -2.32–0.76%) in the < 75 group. A higher risk for cardiovascular mortality was associated with females (1.30% (95% CI 0.14–2.46%)) than with males (0.52% (95% CI -0.63–1.66%)). The risk of cardiovascular and stroke mortality was greater in eastern communities (1.52% (95% CI 0.06–2.98%) and 1.16% (95% CI -0.40% to -2.73%) than in western communities (0.11% (95% CI -2.03–2.24%) and 0.94% (95% CI -0.38–2.26%), respectively). Not surprisingly, central A/C was negatively associated with mortality, with results indicating a 1.04% (95% CI -0.54–2.63%) increase in cardiovascular mortality in the 25th percentile of communities (measured as

prevalence of A/C), compared with a 0.81% (95% CI -0.93–2.61%) increase in the 75th percentile of communities.

As mentioned previously, Klemm et al. (2004) investigated mortality in the elderly population from Fulton and DeKalb counties, GA; no significant association was reported for cardiovascular mortality and PM_{2.5} with a mean daily average of 19.62 µg/m³.

Only two American single-city studies were identified. In New York City, De Leon et al. (2003), using a time-series design, investigated whether or not deaths with secondary respiratory conditions were more affected by air pollutant (PM₁₀, NO₂, SO₂, CO and O₃) exposure than those without such aggravating conditions. Age was considered a modifying factor and the study population was divided in two groups; the mean 24-h average was 33.27 µg/m³. In the >75 years group, a 10 µg/m³ increase in PM₁₀ was associated with an increase of 3.58% in circulatory mortality (95% CI 1.47–5.7%) for individuals with pre-existing secondary respiratory conditions, compared with 1.2% (95% CI 0.65–1.8%) for individuals without secondary respiratory conditions. In individuals with pneumonia, the increase was 4.2% (95% CI 1.0–7.5%) compared with 1.3% (95% CI 0.5–2.0%) in individuals without pneumonia. Finally, individuals with COPD were also at higher risk: an increase of 3.2% (95% CI -0.5–7.0%) compared with 1.4% (95% CI 0.7–2.1%) in individuals without COPD. This effect was generally robust to the addition of a second pollutant in the model; the only exception was the PM₁₀ effect estimate for circulatory death, which became non-significant after inclusion of NO₂ into the model. But, since PM₁₀ and NO₂ were highly correlated (r = 0.73), there still existed a possibility of bias of these estimates.

Moolgavkar (2003) also found statistically significant results in an American two-county study. The strongest association between PM₁₀ and cardiovascular mortality was reported for the summer period at lag 2 d in Los Angeles County, CA, in a single-pollutant analysis (2.0%; no CI given). A significant association was also observed for PM₁₀ in the winter period in Cook County, IL (0.8%; no CI given) at lag 4 d (median daily average of 35 µg/m³). In the whole year period analysis for Cook County, the existing association of PM₁₀ with cardiovascular mortality generally remained stable in a two-pollutant analysis. In Los Angeles County, in a single-pollutant analysis, a 10 µg/m³ increase in PM₁₀ was significantly associated with a 0.5% increase at lag 4 d, while PM_{2.5} was associated with a 0.9% increase in cardiovascular mortality at lag 2 d (median daily average of 44 µg/m³). In two-pollutant models, PM_{2.5} at lag 0 d continued to be associated with cardiovascular mortality after inclusion of CO or NO₂. However, in both locations, the association was generally much stronger for gases (NO₂, SO₂, CO, O₃) than for PM_{2.5} and PM₁₀ metrics (except O₃ in Los Angeles County).

Zeka et al. (2006a) examined the influence of some individual factors on mortality. A 10 µg/m³ increment in PM₁₀ was associated with heart disease mortality, more so in individuals >75 years of age (0.65% (95% CI 0.3–1.00%)) than those <65 (0.04% (95% CI -0.45–0.53%)) (the mean daily average range across cities was 15.9–37.5 µg/m³). A similar pattern was observed for stroke mortality (0.80% (95% CI 0.27–1.33%)) for those >75 years of age and -0.46% (95% CI -1.42–0.50%) for those aged 65–75). This study also found a statistically significant association for location of death (α = 0.05): a 0.15% (95% CI -0.14–0.44%) increase in risk of heart disease mortality for “in hospital mortality” compared with 0.93% (95% CI 0.60–1.26%) for “out of hospital heart disease mortality,” and a 0.06% (95% CI -0.49–0.61%) increase in “in hospital stroke mortality” risk compared with a 0.87% (95% CI 0.05–1.69%) increased risk of “out of hospital stroke mortality.” Among other statistically significant associations was secondary diagnosis as a contributing cause. Regarding this aspect, a 10 µg/m³ PM₁₀ increment was associated with a 1.74% (95% CI 0.35–3.13%) increased risk for stroke mortality when secondary pneumonia was present, compared with a 0.29% (95% CI -0.16–0.74%) increased risk when secondary pneumonia was absent (α = 0.10). The authors suggest these results are

consistent with the findings from a previous study (Goldberg et al., 2000). Some other positive (sometimes significant) associations were also reported by Zeka et al. (2006a): a significant risk for MI mortality was observed in African-Americans, who showed a 0.99% increase (95% CI 0.05–1.93%) as compared with whites, where a non-significant 0.24% increase (95% CI -0.27–0.75%) was found. Women were more at risk for mortality due to stroke than men, with a 0.59% increase (95% CI -0.04–1.22%) and a 0.11% (95% CI -0.58–0.80) risk increase, respectively; a significant association was also observed for MI in women—a 0.59% (95% CI 0.08–1.10%) increased risk compared with a 0.21% (95% CI -0.40–0.82%) increase for MI in men.

This group had previously assessed the effects of lags and modification by city characteristics such as population density, apparent temperature, age standardized mortality rate, proportion of older adults, prevalence of central A/C and proportion of PM from traffic sources using the same exposure data (Zeka et al., 2005). They observed that effect estimates increased significantly with population density, daily minimum summer apparent temperature, daily maximum winter apparent temperature, and proportion of PM from traffic sources. Central A/C, the proportion of older adults and the age-standardized mortality rate did not significantly influence the effect of PM₁₀ on daily mortality. For heart disease mortality, a 10 µg/m³ increase in PM₁₀ was associated with a 0.30% (95% CI 0.05–0.55%) increased risk at lag 2 d and a 0.50% (95% CI 0.25–0.75%) increased risk using 3-d cumulative estimates with an unconstrained distributed lag model. Risks of IHD and congestive heart failure (CHF) mortality were also higher (0.65% (95% CI 0.32–0.98%) using 3-d cumulative estimates and 1.27% (95% CI 0.17–2.37%) at lag 2 d, respectively). The authors concluded that reporting the effect for the greatest estimate of a single day underestimated the true health risks of such exposure.

14.5.1.4.3 European studies

A few European studies focused on associations between PM and cardiovascular mortality; the majority of these studies were multi-city in nature. This is the case of Analitis et al. (2006) who reported results of a study on cardiovascular mortality conducted in 29 European centres using the APHEA database and fixed-site monitoring data. Temperature, humidity, influenza, day of the week and holidays were accounted for, as well as other unusual events, and the median daily average PM₁₀ levels ranged from 9 to 64 µg/m³ across cities. It was observed that 10 µg/m³ increases in PM₁₀ and BS were respectively associated with 0.76% (95% CI 0.47–1.05%) and 0.62% (95% CI 0.35–0.90%) increases in cardiovascular mortality at lag 0–1 d. These risk estimates were elevated to 0.90% (95% CI 0.57–1.23%) and 0.80% (95% CI 0.49–1.11%), respectively, at lag 0–5 d. In two-pollutant models, effects attributed to PM₁₀ and BS generally decreased with the inclusion of SO₂ or NO₂, but remained the same when ozone was included. The percentage increases in mortality associated with both pollutants were greater in cities that were warmer and drier, that had higher long-term average NO₂ levels, greater proportions of older adult individuals and lower age-standardized mortality rates. Estimates of PM₁₀-associated cardiovascular mortality were greatest in southern cities, followed by northwestern and central-eastern cities.

Samoli et al. (2005) examined the shape of the concentration–response relation between PM₁₀ and mortality in 22 APHEA cities, as well as between BS and mortality in 15 of the cities. Penalized regression spline models were developed for each city, and then combined into overall concentration–response curves for both PM₁₀ and BS. These curves were roughly linear in shape for total and cardiovascular mortality. Based on Akaike’s Information Criterion, linear models fit the data much better than threshold models, and slightly better than spline models. There was considerable heterogeneity in the shape of the exposure–response curves across cities, which the authors ascribed in part to differences in the air pollution mix, climate, and the health of the populations.

Biggeri et al. (2005) conducted a multi-city Italian study that explored cardiovascular mortality among other outcomes. A $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with a 1.21% (95% CI 0.32–2.10%) increase using a random effects model, and with a 1.15% (95% CI 0.34–2.11%) increase using a Bayesian approach. In a study of mortality in seven European cities by Touloumi et al. (2005) using various methods to control for influenza epidemics, a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} was associated with elevated risks for cardiovascular mortality ranging from 0.86% (95% CI 0.53–1.19%) to 1.06% (95% CI 0.74–1.39%). The mean daily PM_{10} across cities ranged from 36.5 to $77.6 \mu\text{g}/\text{m}^3$.

In another study conducted in nine major French cities, Eilstein et al. (2004) found non-statistically significant relationships between PM_{10} and cardiovascular mortality at lag 0–1 d and lag 0–5 d; however, statistically significant effects were reported for BS at the same lags (0.5% and 1.2%, respectively) (no 95% CI provided).

Ballester et al. (2002) reported significant effects for PM_{10} , TSP and SO_2 in Spain, with mean city averages ranging from 37.8 to $45.1 \mu\text{g}/\text{m}^3$. Using a random effects model, a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} (lag 0–1 d average) was associated with a 2.4% increased risk of cardiovascular mortality (95% CI 0.1–4.8%) in a two-pollutant analysis including SO_2 .

Few European single-city studies considered short-term cardiovascular mortality. In Italy, Forastiere et al. (2005) carried out a case-crossover study of cardiac mortality over 35 years in residents of Rome. This study estimated an overall risk of 2.8% per $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} for out-of-hospital coronary deaths; this, as the authors mention, is much higher than the NMMAPS and APHEA estimates of 0.2% and 0.6%, respectively (mean daily $\text{PM}_{2.5}$ was $52.1 \mu\text{g}/\text{m}^3$). In single-pollutant analyses, a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} was significantly associated with coronary death at lag 0, lag 0–1 and lag 1 d (1.59% (95% CI 0.03–3.2%), 2.01% (95% CI 0.2–3.9%) and 1.62% (95% CI 0.0–3.29%), respectively). The concentration–response curve showed a quasilinear trend for PM_{10} and revealed no threshold. In addition, a stronger effect was observed among the older adults. In a time-series study conducted in Bordeaux, France, Filleul et al. (2004a) found a statistically significant association between BS and cardiovascular mortality, with a mean level of BS during the exposure period of $17.6 \mu\text{g}/\text{m}^3$. Temporal trend, seasonal effects, influenza epidemics, temperature, humidity and day of the week were controlled for. In the all-age population, a $10 \mu\text{g}/\text{m}^3$ increase in BS was associated with a 2.3% mortality increase (95% CI 0.1–4.6%) in the 2-d moving average (lag 0–1 d) model, using a penalized spline to control for confounders.

Another study led by Filleul and conducted in Bordeaux, France (using the same exposure data), focused on the older adult population; its purpose was to identify characteristics that could confer higher risk to individuals exposed to BS (Filleul et al., 2004b). This analysis revealed many statistically significant associations for cardiorespiratory mortality at lag 3 d, with a 30% (95% CI 1–68%) increased risk for the entire population, 52% (95% CI 3–125%) in the ≥ 84 age group, 336% (95% CI 15–1554%) in individuals with a secondary school education or higher, 62% (95% CI 7–145%) in single or widowed individuals, 42% (95% CI 3–94%) in individuals not confined in the house, 78% (95% CI 17–171%) in individuals with dyspnea, and 66% (95% CI 5–162%) in individuals with angina. Also in Bordeaux, Lepeule et al. (2006) conducted a survival analysis of an older adult cohort. This type of analysis was proposed as an alternative approach to cohort studies. Statistically significant associations were found for cardiorespiratory mortality and air pollution at lag 3 d (with a 24% increased risk (95% CI 4–47%) per $10 \mu\text{g}/\text{m}^3$ increase in BS). This risk was higher in current smokers (85% (95% CI 18–189%)) than in ex-smokers (75% (95% CI 3–216%)). The authors report that these findings are similar to the results from Filleul et al. (2004a) and suggest that survival analysis could be useful for short- and long-term studies of the health effects of air pollution. Filleul et al. (2006) also investigated the effect of using proximity to ambient air monitors rather than to background

monitors in the cardiovascular mortality association with BS in Le Havre, France, from 1994 to 1997. The mean daily BS concentration range across six monitoring stations was 8.53 to 13.76 $\mu\text{g}/\text{m}^3$. The risk of cardiovascular mortality differed depending on the type of monitoring data used; a 10 $\mu\text{g}/\text{m}^3$ increase in BS was associated with a 3.75% (95% CI -1.142–9.19%) increased risk using background station measurements and a 4.72% (95% CI -0.62–10.34%) risk using a balance of background and close proximity station data.

In Nis, Serbia, Bogdanovic et al. (2006) found a statistically significant association between BS and cardiovascular mortality (1.25% (95% CI 0.53–1.97%) per 10 $\mu\text{g}/\text{m}^3$ increase in BS) at lag 0 d (mean daily average BS 23.04 $\mu\text{g}/\text{m}^3$). In the same year, Stolzel and collaborators reported on the effects of various PM size fractions on cardiopulmonary mortality in Erfurt, Germany (Stolzel et al., 2007). An association was observed between $\text{NC}_{0.01-0.1}$ (IQR = 9748 particles) and cardiorespiratory mortality (with a 3.1% increase (95% CI 0.3–6.0%)) at lag 4 d. Positive and significant results were also measured with other UFP size fractions ($\text{NC}_{0.01-0.03}$; $\text{NC}_{0.03-0.05}$; $\text{NC}_{0.05-0.1}$) whereas by contrast, PM mass concentration was not associated with any significant effect on cardiorespiratory mortality. Mean daily average PM_{10} and $\text{PM}_{2.5}$ concentrations were 32.3 $\mu\text{g}/\text{m}^3$ and 21.7 $\mu\text{g}/\text{m}^3$, respectively. These results suggest a higher risk associated with smaller particles.

In the Netherlands, Fischer et al. (2003) reported a statistically significant association between BS and CVD mortality in individuals 65–74 years old (4.0% increase (95% CI 0.6–7.5%)), in those ≥ 75 years of age (3.0% increase (95% CI 0.1–5.1%)) but not in individuals aged 45–64 (0% increase (95% CI -4.3–4.6%)) and in those < 45 (5.7% increase (95% CI -6.6–19.6%)). PM_{10} -associated risks were all non-significant, with a median distribution of daily concentrations of 34 $\mu\text{g}/\text{m}^3$.

In metropolitan Helsinki, Finland, Penttinen et al. (2004) reported no consistent effect of PM_{10} exposure (median daily average 21 $\mu\text{g}/\text{m}^3$) on cardiovascular mortality; the highest positive PM association was non-significant (0.63% (95% CI -1.09–2.35%) at lag 1 d per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10}). Particulate pollutant values were provided by three fixed ambient air monitors, with PM_{10} measurement every fourth day and TSP measurement every second day.

14.5.1.4.4 Australian studies

Only one study that considered acute cardiovascular mortality was carried out in Australia (Simpson et al., 2005). The focus of this study was all-cause, respiratory and cardiovascular mortality in four major Australian cities. Mean 24-h PM_{10} and $\text{PM}_{2.5}$ varied across cities (16.30–18.20 $\mu\text{g}/\text{m}^3$ and 7.5–9.3 $\mu\text{g}/\text{m}^3$, respectively). Associations between PM_{10} or $\text{PM}_{2.5}$ and mortality were not statistically significant in a meta-analysis of the cities with sufficient data available for each pollutant. However, acute cardiovascular mortality was significantly associated with increases in 24-h bsp (IQR averaged over d 0–1) at lags 1, 3 and 0–1 d, with increases of 4.39% (95% CI 0.9–8.0%), 4.3% (95% CI 0.9–7.9%) and 4.8% (95% CI 0.8–9.0%), respectively.

14.5.1.4.5 Other studies

Fourteen studies were identified that evaluated the effect of PM_{10} primarily on total cardiovascular mortality under exposure conditions dissimilar to Canadian environments. In a Japanese time-series study, Omori et al. (2003) studied older adult populations in 13 major cities, revealing a significant association between SPM and cardiovascular mortality. In Seoul, South Korea, Kim and Yang (2005) conducted a 1-year time-series study that revealed a positive non-statistically significant association between PM_{10} and cardiovascular mortality in individuals > 65 at lag 2 d. In other time-series studies PM_{10} was associated with daily cardiovascular mortality in Shanghai, China (Kan and Chen, 2003a), and was positively, but not

significantly associated with daily cardiovascular mortality in Bangkok, Thailand (Vajanapoom et al., 2002) and Chongqing, China (Venners et al., 2003).

The results of case-crossover studies were more varied. An association between PM₁₀ and daily cardiovascular mortality was observed in Shanghai (Kan and Chen, 2003b), while only non-significant negative associations were observed in Kaoshiung, Taiwan (Tsai et al., 2003a) and no associations were observed in Taipei, Taiwan (Yang et al., 2004b). With respect to the effects of Asian dust storms, in Taipei, Chen et al. (2004a) found a positive non-statistically significant effect of PM from dust storms on cardiovascular mortality 2 d after the event, while in Seoul, Kwon et al. (2002) found that PM₁₀ from dust storms was positively associated with cardiorespiratory mortality in the whole population using a 3-d moving average.

A small number of studies investigated more specific mortality outcomes. A study by Kan et al. (2003) reported a significant association between stroke mortality and PM₁₀; however, this association became non-statistically significant in multi-pollutant analyses. In Hong Kong, Wong et al. (2002) found a significant association between PM₁₀ and IHD mortality, and non-significant increases for cardiovascular mortality and cerebrovascular mortality; the relation for IHD mortality became non-significant in multi-pollutant analyses with SO₂, O₃ and NO₂.

Recent work has suggested that some PM effects could occur at shorter time periods than the 24-h period that is typically considered in most analyses. In a time-series study that evaluated 1990–1994 data from Tokyo, Japan, Murakami and Ono (2006) assessed MI mortality associated with hourly exposure to high levels of SPM (mainly equivalent to PM₇). Poisson regression models were adjusted for the period before death, average temperature, hour of the day and region where death occurred (city or suburb). Some highly significant rate ratios were reported in the two lowest concentration groups, with higher risks for shorter windows of exposure. There was a general trend in increasing risk with increased concentration, and in the highest quartile very high non-significant adjusted rate ratios were calculated for each hour of exposure between 1 and 6 h.

Results from another study also suggested that very short exposure windows may result in significant risks. This case-crossover study was published by Yamazaki et al. (2007) and involved an evaluation of the effects of centrally monitored SPM (PM₇) on intracerebral haemorrhage and ischemic stroke mortality in the older adults (≥65 yrs) inhabiting 13 major urban areas of Japan between 1990 and 1994. A time-stratified approach was used with controls for long-term trends, seasonality, daily temperature, humidity, day of the week, and circadian rhythm; separate analyses were done for hourly and daily values. This model was also used to calculate intracerebral haemorrhage and ischemic stroke ORs for a 30 µg/m³ PM₇ increase for various lagged 24-h PM₇ average concentrations, after adjustment for daily NO₂, temperature and humidity. Another model was developed to evaluate the effect of short windows of exposure on the risk of stroke mortality, using the NAAQS for a PM₇ hourly value (200 µg/m³) as a threshold. Lags of up to 5 h were explored. Analyses were done for warm and cold seasons. A significant association was observed between the PM₇ 1-h average concentration over 200 µg/m³ and intracerebral haemorrhage: a 4.4% increase (95% CI 2.0–7.0%) per 10 µg/m³ increase in PM₇ at lag 2 h in the warmer months. This relationship was not observed using a 24-h average of PM₇.

14.5.1.5 Summary and Considerations: Acute Mortality

Overall, this review of approximately 70 acute mortality studies published between 2002 and 2006 provided evidence of an association between acute exposure to PM and mortality. Recent studies have contributed to our understanding of the mortality effects associated with acute exposure to PM. A majority of these studies have reported positive findings, most of which were statistically significant. In studies conducted in North America, the increased risk for total

mortality ranged approximately between 0.1 and 3% per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} and from 0.7 to 5.6% for $\text{PM}_{2.5}$ (figures 14.13 and 14.14). PM-associated excess risks were generally similar or greater in studies that investigated categories of mortality, particularly respiratory mortality (0.07–0.9% for PM_{10} and 1.8–7.5% for $\text{PM}_{2.5}$) (figures 14.15 and 14.16) and cardiovascular mortality (0.3–3.6% for PM_{10} , and 0.6–11.4% for $\text{PM}_{2.5}$) (figures 14.17 and 14.18). Several studies have also examined specific subcategories of respiratory or cardiovascular mortality such as pneumonia, stroke, MI, COPD, IHD or CHD.

Only a handful of Canadian mortality studies (Vedal et al., 2003; Villeneuve et al., 2003; Burnett et al., 2004; Jerrett et al., 2004; Goldberg et al., 2006) investigated the association between acute exposure to PM air pollution and mortality. While consistently positive and mostly significant associations with total, respiratory or cardiovascular mortality were found for various PM metrics, there was sometimes sensitivity to the inclusion of co-pollutants with the PM association often reduced. The only Canadian multi-city study (Burnett et al., 2004) found strong PM associations in single-pollutant models (for one in six day values of PM), but these associations became non-significant after the inclusion of NO_2 . Importantly, when the study utilized the more limited dataset for every-day (TEOM) PM monitoring, the NO_2 risk was substantially reduced and became non-significant in two-pollutant models, while the $\text{PM}_{2.5}$ risk estimate was only marginally reduced and remained statistically significant. In addition, most studies were performed in a single city and would therefore have had limited statistical power, which likely contributed to the non-significant findings in some of the studies. Other notable findings include the study performed in Montreal (Goldberg et al., 2006) where a strong association was found between $\text{PM}_{2.5}$ and both diabetes mortality and all-cause mortality in diabetics, and the Hamilton study (Jerrett et al., 2004) where the PM-associated effect was modified by the socioeconomic characteristics of the population.

Additional evidence for an association between acute exposure to PM and mortality is also provided by multi-city studies. These studies are less prone to biases affecting smaller studies and are believed to generate more stable results. The NMMAPS in the US has provided a wealth of information on the acute health effects of exposure to air pollution. In more recent literature, researchers have investigated this database in more detail. In two NMMAPS studies, PM_{10} was associated with cardiovascular/respiratory mortality, an effect that was greater than total mortality or other-cause mortality. This association generally occurred at lag 1 d and was stronger in the northeast and in California than other areas of the country. When NMMAPS data were analyzed for potential biases associated with GAMs, it was concluded that there was little sensitivity to different data treatments (e.g. GAM vs. GLM). Seasonal analyses seemed to indicate that PM effects on mortality were significant all year round as well as in the summertime. Welty and Zeger (2005) studied whether seasonality and weather were contributing to an artificial association between PM_{10} and mortality and found that they were not. Other models were developed and tested with NMMAPS data to address sampling frequency error and potential misclassification error, and results were robust to these issues.

A number of population health studies have examined whether there are thresholds for the mortality associated with short-term exposure to PM. Approaches have included fitting alternative models to describe concentration–response relationships, or segregating high from low pollutant days to determine if risk estimates differ. Applying these methods to the results of a number of large US and European multi-city studies, including those reviewed in the US EPA 2004 AQCD and this assessment (Daniels et al. 2004; Schwartz 2004a; Samoli et al. 2005; Forastiere et al. 2005), has revealed no evidence of a clear threshold for acute exposure PM-related mortality. Instead, in these studies total and cardiorespiratory mortality were observed to increase monotonically with increasing PM concentrations, even at relatively low PM levels. In instances where formal statistical tests were applied, they consistently indicated that a linear

Figure 14.13 Risk estimates for total mortality per 10 µg/m³ increase in PM₁₀ concentration in single-pollutant models

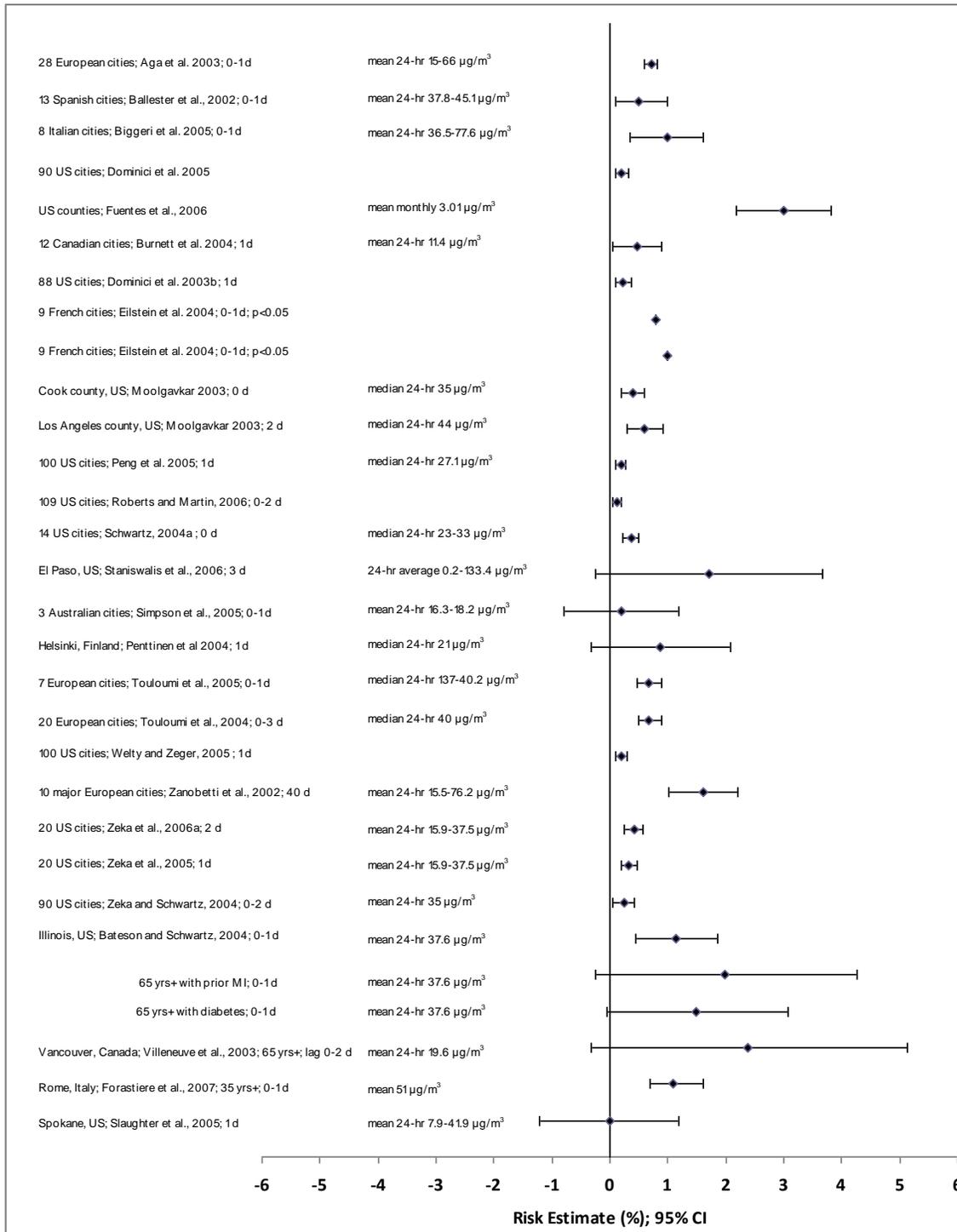


Figure 14.14 Risk estimates for total mortality per 10 $\mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ concentration in single-pollutant models

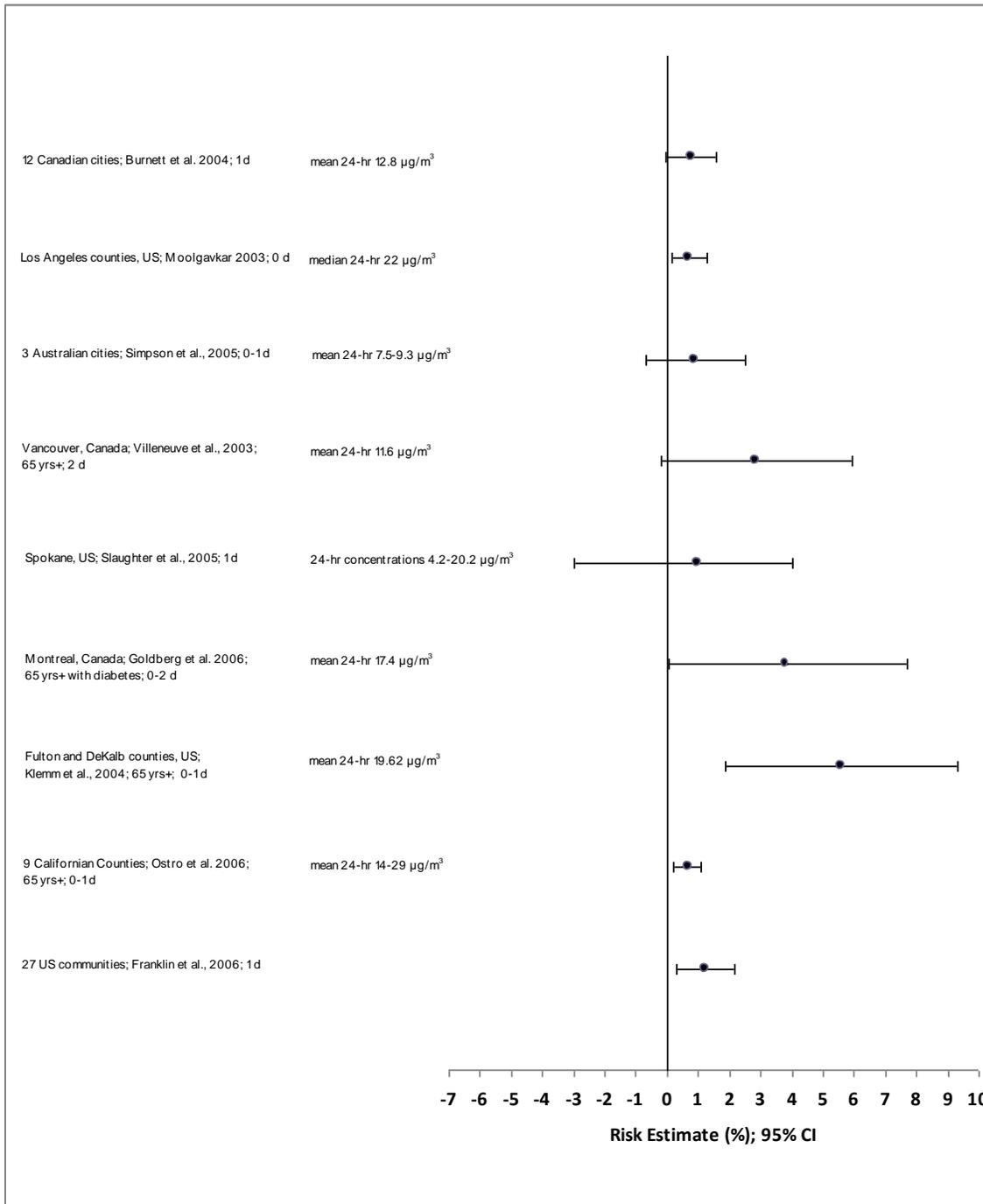


Figure 14.15 Risk estimates for respiratory mortality per 10 µg/m³ increase in PM₁₀ concentration in single-pollutant models

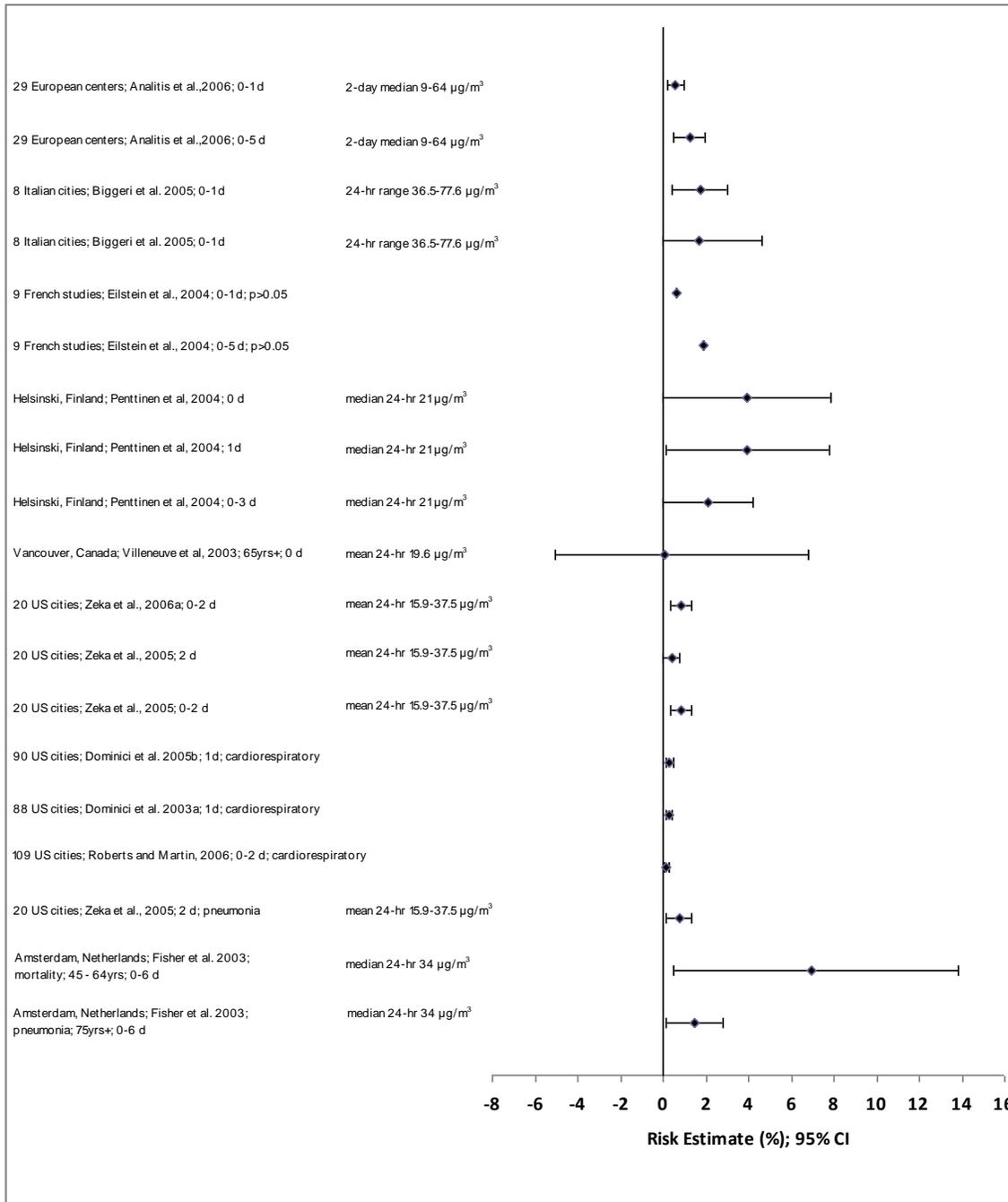


Figure 14.16 Risk estimates for respiratory mortality per 10 µg/m³ increase in PM_{2.5} concentration in single-pollutant models

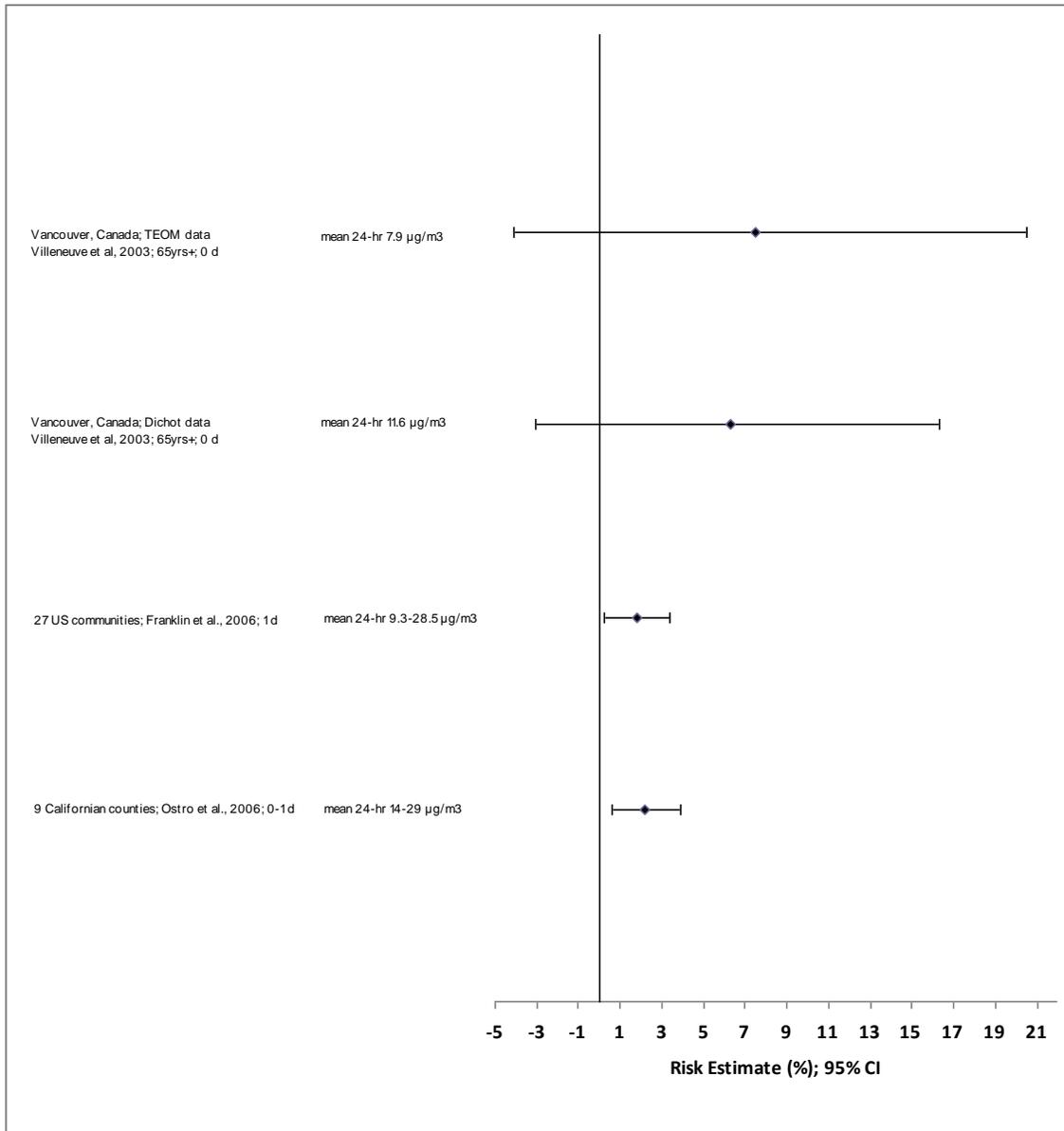


Figure 14.17 Risk estimates for cardiovascular mortality per 10 µg/m³ increase in PM₁₀ concentration in single-pollutant models

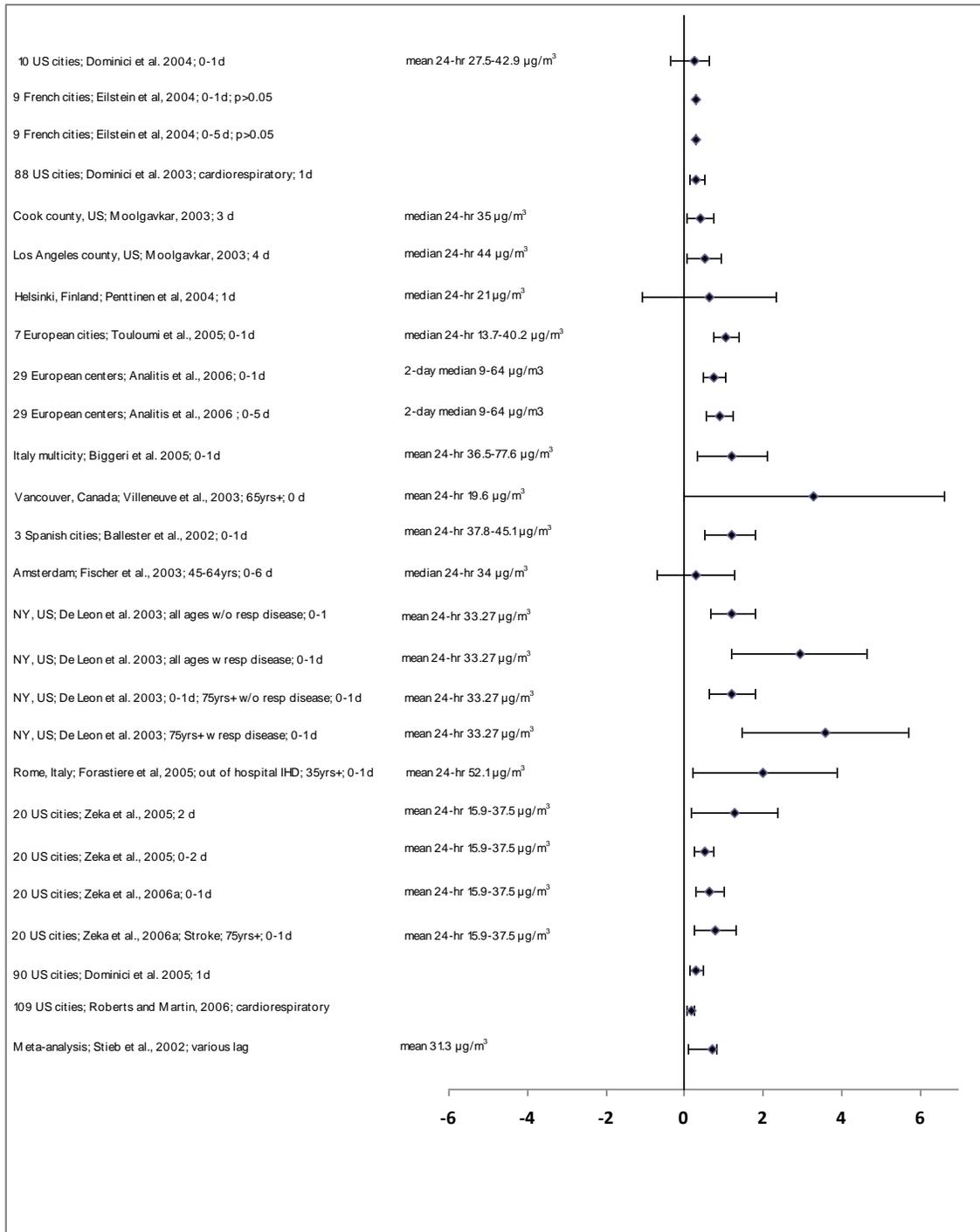
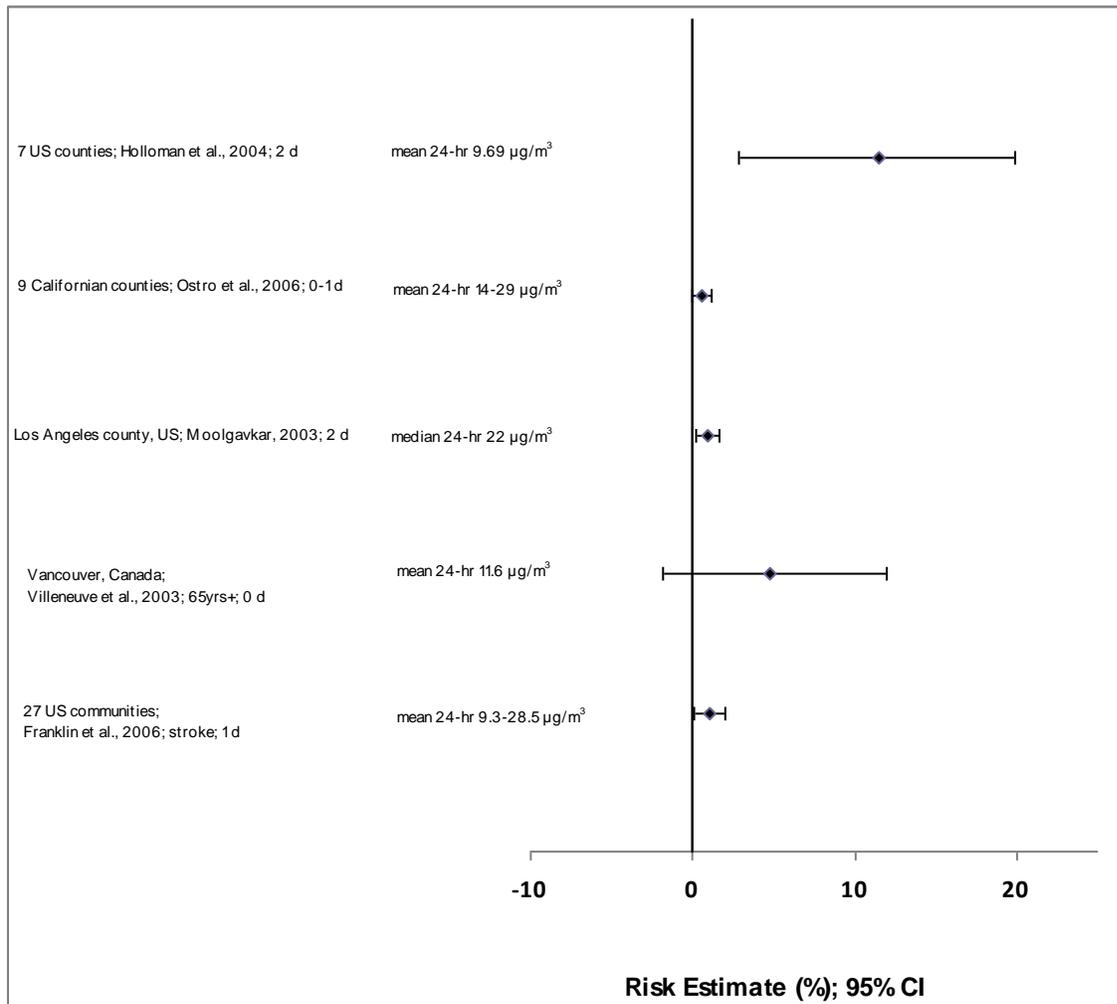


Figure 14.18 Risk estimates for cardiovascular mortality per 10 µg/m³ increase in PM_{2.5} concentration in single-pollutant models



concentration–response model was preferred over other models, including spline and threshold models.

Several groups have reported stronger effects in subsets of the population. The most commonly reported factors in the recent literature were pre-existing conditions, age, gender and geography. A range of pre-existing conditions (e.g. dyspnea, angina, stroke) have been implicated in stronger associations between PM and mortality but only in one or a limited number of studies. By contrast, the association of air pollution with all-cause mortality for diabetics was observed in three independent studies. In one study (Goldberg et al., 2006), both diabetes mortality and all-cause mortality in diabetics were significantly associated with PM air pollution in Montreal. With respect to age, several studies have found associations between acute exposure to air pollution (PM_{2.5}, PM₁₀ and BS) and all-cause, respiratory or cardiovascular mortality in older adults. In some studies these effects were stronger in cities that had a higher proportion of older adult citizens. In one study the association between PM₁₀ and heart disease mortality was greater in individuals >75 years of age than in those <65. Interestingly, Ostro et al. (2006) showed that the association between PM and all-cause mortality in older adults was not

affected by the inclusion of gaseous pollutants in their model, whereas addition of these pollutants did affect estimates in other age groups. The most detailed study on age stratification (Fischer et al., 2003) showed that effects on mortality appeared in persons >45 years of age (45–64, 65–74 and ≥75) but not in the younger population (<45). It is not known, however, whether this is simply an effect of the relative absence of mortality in this younger age group (and the resultant lack of power to see a small effect in a small sample size) or of the relative absence of susceptible disease states. While differences have been reported between men and women, overall these results are equivocal. Although there may be weak evidence that women are more at risk for cardiovascular-related mortality (MI, stroke (non-significant association), cardiovascular), there is also conflicting evidence as to which gender may be more susceptible to all-cause and cardiorespiratory mortality. With respect to geography, results from analyses of the NMMAPS database have consistently suggested that mortality effects may be greater in the northeast, and sometimes in California, compared with other areas of the country. In a European study effects were stronger in the south than in the northwest or central east. There was limited evidence that mortality effects were greater in warmer and drier cities. Whether this helps to explain geographical differences or is simply a surrogate for time spent outdoors requires further investigation.

In addition, stronger PM effects have been related to low income, prevalence of A/C, higher long-term NO₂ concentrations, percentage of traffic-related PM, population density and ethnicity, although these have been reported less frequently. One French study found several contributing factors depending on the cause of mortality (e.g. widowed, single, secondary education, not confined to the house, blue collar). In the Zeka et al. study (2006a), education, a proxy for SES, was found to be inversely associated with daily mortality; in Hamilton, ON, Jerrett et al. (2004) also reported significant associations between education and mortality. Similar results were also reported by Martins et al. (2004) who observed an association of mortality with poverty, even if this association was not statistically significant.

Ambient PM exposure is accompanied by exposure to other air pollutants, some of which are closely correlated because they are emitted by common sources, subject to dispersion by common factors, and may even be in the pathway of PM formation (e.g. SO₂ giving rise to sulphate particles). Many of the short-term studies have examined the impact of adjusting for co-pollutant exposure on PM-mortality associations. For most of the studies reviewed in the US EPA 2004 AQCD and in this assessment, the risk estimates for PM₁₀, PM_{2.5} or BS were fairly robust to adjustment for other pollutants. While the estimates were sometimes reduced in models that included gaseous pollutants (particularly NO₂, which is often highly correlated with PM and indeed is ultimately converted to particulate nitrates), they remained positive and most often statistically significant. This is particularly clear in the findings for total mortality in multi-city studies or meta-analyses, whereas the findings for PM in some of the single-city studies or studies of more specific and less common causes of mortality (e.g. Wong, 2002; Kan et al., 2003) were more affected by adjustment for various other pollutants

The mortality displacement hypothesis, though difficult to study, has been explored using data from the US and Europe with different statistical methods (distributed lag models, frequency domain, moving average approaches). Several papers on this topic were published in earlier years (Zeger et al., 1999; Samet et al., 2000; Zanobetti et al., 2000; Schwartz, 2000, 2001) while fewer studies have been carried out in the period covered here (Zanobetti et al., 2002; Dominici et al., 2003). As was the case with the earlier reports, the results of these more recent studies indicate that the effects observed in daily time-series are not primarily attributable to short-term mortality displacement, but rather extend over a period of weeks to months. Over the years, several studies using different approaches have produced generally similar and consistent results, which do not support the mortality displacement hypothesis; a thorough

analysis of this issue by the US EPA (2004) concluded that there was no evidence to support the hypothesis of a time-restricted effect of PM exposure on mortality.

Even though the great majority of the studies have relied on ambient air monitors to reflect individuals' exposure to PM health effects, some researchers have developed techniques to reflect more precise exposure estimates. Jerrett et al. (2004) used Thiessen polygons to identify five areas in Hamilton, ON, with an ambient air monitor as a central nodal point in each area. Proximity to a monitor has also been used as a proxy for exposure by Filleul et al. (2006). Forastiere et al. (2007) used exposure distribution to explore the association of four ranges of PM emissions with mortality. Holloman et al. (2004) compared risk estimates for cardiovascular mortality based on modelled population exposure to PM_{2.5} with estimates using ambient concentrations. Most of these studies reported higher risk estimates for the more refined exposure measures compared with concentrations measured at a central ambient monitor; however, Filleul et al. (2006) concluded that proximate monitors did not significantly modify the risk estimate that was obtained using background monitoring stations.

14.5.2 Hospital Admissions

Hospital admissions represent one of the key health indicators used to assess the effects of environmental factors such as air pollution on human health, since admissions data are collected and managed in standard databases. However, because databases are often implemented for purposes other than public health surveillance, they may be limited by deficiencies that reduce their capacity to be used in epidemiological analyses. Generally, individuals who require hospitalization represent a small, but seriously ill, subset of all individuals who may be affected by air pollution. However, admissions are affected by a number of factors aside from the severity of morbidity, such as the availability of beds and the criteria for admission (which will vary between individual physicians and between health care systems). As a result, it can be anticipated that risk estimates for hospital admissions may be more heterogeneous and have greater variance than those for other health indicators, such as mortality.

14.5.2.1 Summary of Previous Assessments

The 1999 PM SAD reviewed 16 hospital admission studies covering North America and Europe. In single-pollutant analyses, all 16 studies found positive and significant associations between PM₁₀ (the most widely used metric at that time) and hospital admissions. In studies that examined multi-pollutant or bivariate relationships, PM₁₀ remained positively associated, though in some instances the relationship lost statistical significance. The high correlation between pollutants was the major explanatory factor in these studies. The major findings were with respiratory outcomes, while the few studies examining cardiac endpoints also found significant relationships (though always less in magnitude than the respiratory ones). Variable evidence was presented about population groups representing potentially susceptible subgroups. For groups with respiratory disease (COPD, asthma) there was only limited evidence of greater effects, though this may have been due to the greatly reduced sample size for these. Inconsistent results were found when considering age (elderly, children). Overall, the 1999 PM SAD concluded that PM represented the most stable and consistent predictor of air-pollution-related hospital admissions.

The US EPA 2004 PM AQCD reviewed a significant number of new hospital admission studies and noted a great increase in those addressing cardiac outcomes. Among these cardiac studies, many indicated an independent effect of fine PM, while another body of studies that found a fine PM effect could not draw definitive conclusions as to whether or not the effect was

independent of co-pollutants. For the relatively small number of studies that addressed specific cardiac endpoints, it was noted that IHD (the major cause of heart disease) exhibited much greater risk estimates than others. For respiratory endpoints, results were noted as being very consistent with the US EPA 1996 PM AQCD, where PM was found to be consistently associated with these outcomes. In studies examining specific endpoints, asthma associations with hospital admissions were noted as exhibiting somewhat higher risk estimates than those for other conditions such as COPD and pneumonia. Additionally, it was noted that the evidence was compelling for both the fine and coarse fractions of PM₁₀.

14.5.2.2 Respiratory Admissions

A total of 25 studies published between 2002 and 2006 originating from North America (13), Europe (4), Australia (4), and South America and Asia (4) were reviewed. The majority of studies (16) were time-series in design; 7 others were case-crossover, 1 used both case-crossover and time-series approaches, and 1 was a case-control type. Single-pollutant analyses were performed in 18 studies; both single and multi-pollutant analyses were carried out in 9 studies. Most studies (15) used PM₁₀ as a primary PM metric, while 12 studies investigated the effects associated with PM_{2.5}.

14.5.2.2.1 Canadian studies

Among the seven Canadian studies that were reviewed, several different outcomes were studied in subjects ranging from infants to older adults using both time-series and case-crossover designs. One recent study compared the results from time-series techniques with those from case-crossover designs. Luginaah et al. (2005) investigated the relationship between respiratory hospital admissions and air pollutants (PM₁₀, NO₂, SO₂, CO, O₃, COH and total reduced sulphur) in Windsor, ON, using both time-series and case-crossover designs. The time-series analysis accounted for day of the week, temperature, humidity and air pressure. The case-crossover analysis was bidirectional in design, with 2 weeks between case and control periods, and used conditional logistic regression with a Cox proportional hazards model. The same covariates were used in both analyses. The mean daily concentration of PM₁₀ was 50.6 µg/m³. In the time-series analysis, a 0.5 COH unit (corresponding to the IQR) was associated with respiratory hospitalizations at lag 3 d (a 6.7% risk increase (95% CI 0.4–13.5%)) in all females, and a 10 µg/m³ increase in PM₁₀ was associated with respiratory hospitalizations in males aged 15–64 at lag 2 d (5.34% (95% CI 1.15–9.7%)). At the same lag, COH was also associated with respiratory hospitalizations in females aged 15–64 (a 15.0% increase (95% CI 0.2–29.6%)). In the case-crossover approach, the same increment in COH was associated with a 19.6% increase (95% CI 0.3–42.6%) at lag 2 d and a 28.9% increase (95% CI 5.1–58.2%) at lag 3 d in the female group 15–64 years of age. The risk estimates for PM₁₀ and COH were consistently positive for females of all ages, 0–14 years, and 15–64 years, though most of these were not statistically significant.

The only recent Canadian study of respiratory hospitalizations in children suggested that boys were more likely to be hospitalized for respiratory infections than girls. Lin et al. (2005) used a case-crossover design to study air pollution and respiratory infection in Toronto-area children. The target population included boys and girls less than 15 years of age who had been admitted for lower respiratory infections (laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonia and influenza). The results were considered for 1–7 d lagged average exposure, and the mean daily average PM₁₀ and PM_{2.5} levels were 20.41 and 9.59 µg/m³, respectively. For a 6-d exposure averaging, an increase of 10 µg/m³ in PM₁₀ was associated with hospital admissions for boys and girls after adjusting for meteorological factors and gaseous pollutants (a 15.7% increase (95% CI 0.8–32.4%)). This effect remained significant in boys (a 19.5% increase (95% CI 0.8–41.3%)), but not in girls. PM_{10-2.5} was also significantly associated with hospital admissions in

boys and girls, both in combination and separately, after inclusion of gaseous pollutants, whereas the risk estimates with PM_{2.5} were not significant and were mostly not positive.

Several Canadian studies have investigated hospitalizations due to exposure to air pollution in older adults. In the only case-crossover study, Fung et al. (2006) investigated respiratory hospitalizations in older adult Vancouver residents using a bidirectional approach. For recurrent event data they found marginally significant results associated with COH, PM₁₀ and PM_{10-2.5} in the three approaches that were considered: first using a method that was developed by Dewanji and Moolgavkar (2000), second with a time-series method and third with a case-crossover method. Stronger results were found for lags 0 and 3 d (using time-series methods, increased risk was 2.0% (95% CI -0.1–4.1%) for PM₁₀ at 0d, and 4.9% (95% CI 0.75-9.1%) for PM_{10-2.5} at lag 3d); smaller, non-significant results were obtained for PM_{2.5}. The mean maximum daily levels of PM₁₀ were 38 µg/m³.

Two studies of the effects of air pollution on COPD hospitalizations among older adults in Vancouver concluded that it was difficult to separate the effects of single pollutants from the combined effects of multiple pollutants. In a time-series study design, Yang et al. (2005) investigated the air pollutants CO, NO₂, SO₂, O₃ and PM₁₀; adjustment for long-term trends was performed by regressing a number of acute COPD daily hospital admissions using a natural logarithm on the natural spline of day of study. Weather (temperature and humidity) and day of the week were also included in the model, and the mean daily average concentration of PM₁₀ was 14.02 µg/m³. In a single-pollutant analysis, an increase of 10 µg/m³ in PM₁₀ was associated with COPD hospitalizations at several lags: 1 d, 8.5% (95% CI 3.6–14.7%); 2 d, 9.8% (95% CI 3.6–15.9%); 3 d, 11.0% (95% CI 3.6–19.7%); 5 d, 12.2% (95% CI 3.6–20.9%); 6 d, 14.7% (95% CI 6.1–24.7%); and 7 d, 15.9% (95% CI 6.1–25.9%). In two-pollutant models, the same increment of PM₁₀ was associated with increases of 15.9% (95% CI 6.1–25.9%) and 18.4% (95% CI 6.1–25.9%) at lag 7 d when modelled with ozone and SO₂ respectively.

In an earlier time-series study, Chen et al. (2004b) used GLMs to study the influence of particulate air pollution on COPD hospital admissions, with parametric natural cubic splines to remove temporal trends and seasonal and sub-seasonal cycles in COPD hospitalizations. In single-pollutant models, they found that the 3-d average concentration adjusted risks corresponding to an increment of 10 µg/m³ for PM₁₀ and PM_{2.5} were 16.5% (95% CI 6.9–27.0%) and 20.9% (95% CI 4.0–40.6%) respectively; a 5% (95% CI 1.2–9.0%) risk increase was also reported for a COH IQR increase. In two-pollutant models, the associations between PM₁₀ and COPD hospitalizations remained significant when PM_{2.5} or COH were included, with 20.1% (95% CI 3.0–39.9%) and 17.1% (95% CI 2.3–34.1%) increases per 10 µg/m³ respectively. When PM_{10-2.5} was included in the models with PM₁₀, the risk estimate for PM₁₀ was slightly reduced and no longer significant. Two-pollutant models including PM_{2.5} and PM_{10-2.5} showed that both elements were associated with COPD admissions. When gaseous pollutants were modelled with PM₁₀, significant risk increases per 10 µg/m³ increase were reported as 13.9% (95% CI 0.5–29.0%) with CO, 17.3% (95% CI 7.4–28.0%) with ozone, and 14.1% (95% CI 1.6–28.1%) with SO₂. PM_{2.5} was no longer significantly associated with COPD admissions when modelled with gaseous pollutants, except with ozone, where a change of 22.3% (95% CI 5.1–42.7%) was noted for an increase of 10 µg/m³ in PM_{2.5}. The mean daily concentrations of PM₁₀ and PM_{2.5} were 13.31 and 7.7 µg/m³, respectively.

The same group also explored the relationship between air pollution and respiratory hospital admissions on first and second visits, and on overall admissions of older adults (≥65 years) using the same environmental data (Chen et al., 2005b). This study revealed no consistent statistically significant association between PM_{2.5} or PM₁₀ and respiratory admissions of the older adults. Finally, in a time-series study (Fung et al., 2005b) conducted in London, ON,

hospital admissions for respiratory outcomes were split into asthma and non-asthma diseases. For same-day and 2-d PM₁₀ averages, a 10 µg/m³ PM₁₀ increase was associated with increases of 9.0% (95% CI 1.1–17.6%) and 9.3% (95% CI 2.0–17.1%), respectively, in asthma admissions among adults aged >65. The mean daily average PM₁₀ concentration was 38 µg/m³.

14.5.2.2 US studies

An important time-series study was published by Dominici et al. (2006), who examined hospital admissions for cardiovascular and respiratory disease in older adults. This study was the largest ever conducted in the US to assess national and regional fine PM health effects on cardiovascular and respiratory disease hospital admissions. The study was carried out in 204 US counties with populations larger than 200,000 clustered into 7 geographical regions; air pollution data were collected from a national monitoring network. Daily hospital admissions data were compiled for CHF, heart rhythm disturbance, cerebrovascular events, IHD, COPD, respiratory tract infection and injury. The study population resided an average of 5.9 miles (approx. 9.6 km) from a PM_{2.5} monitor. The following potential confounders were adjusted for: day of the week, seasonality, influenza epidemics and change in medical practice, temperature and humidity. The average of the counties' mean annual PM_{2.5} values was 13.4 µg/m³. The reduction in annual hospital admissions for cause-specific disease associated with a 10 µg/m³ decline in PM_{2.5} was also assessed. The results from this analysis revealed significant homogeneity of PM_{2.5} concentrations across regions, but possible spatial heterogeneity of effects on various health outcomes. The authors suggested that sources and the mix of ambient pollutants may play a role in these variations. Formal tests of heterogeneity found that the heterogeneity was not significant, although the authors acknowledged that the power to statistically observe the phenomenon may have been lacking. The strongest respiratory effects were observed at lags 0 and 1 d for COPD admissions and lag 2 d for respiratory tract infection admissions, and these effects were stronger in the west than the east. Finally, temperature was observed to modify the effect of pollutants on two respiratory outcomes. Across all counties at lag 0 d a 10 µg/m³ increase in PM_{2.5} was associated with increased COPD admissions, a 1.61% increase overall (95% CI 0.56–2.66%), a 0.91% increase in all Medicare enrollees (95% CI 0.18–1.64%) and a 1.47% increase in individuals ≥75 years of age (95% CI 0.54–2.40%). For respiratory tract infections at lag 2 d the increase was 1.39% overall (95% CI 0.60–2.09); the increase was also significant at 0.92% or 0.93% for Medicare enrollees >65, as well as in individuals aged 65–74 or those >75.

Again in the US, Medina-Ramon et al. (2006) published the results of a case-crossover study of hospital admission data for COPD or pneumonia in older adults living in 36 cities. Conditional logistic regression models were used to investigate city-specific effects, controlling for day of the week and weather; an additional analysis was completed with stratification by season (warm vs. cold). The overall mean 24-h concentration was 30.4 µg/m³. In the warm season, a 10 µg/m³ increase in PM₁₀ was associated with a 1.47% increase in COPD hospitalizations (95% CI 0.93–2.01%) at lag 1 d and with a 0.84% increase for pneumonia (95% CI 0.50–1.19%) at lag 0 d. Associations at lag 0 and 1 d for COPD and pneumonia, respectively, were weaker but significant. When the warm and cold seasons were considered together, these results weakened further but still remained significant. During the cold season, the only important finding was an association with pneumonia at lag 0 d (0.30% (95% CI 0.07–0.53%)). When comparing the 25th and 75th percentiles of cities according to percentage of households with central A/C, an increase of 10 µg/m³ PM₁₀ was associated with significantly fewer admissions for pneumonia at the 75th percentile than the 25th (-0.11% vs. 1.47%).

A case-crossover study designed by Karr et al. (2006) examined hospitalization for bronchiolitis in infants from the South Coast Air Basin of California. Fine particle data were extracted from the State of California's fixed monitoring database; individual exposure was then estimated

based on ambient monitor data and residential ZIP code centroids mapped to the nearest monitoring station (mean daily PM_{2.5} chronic and subchronic exposure was 25 µg/m³). The analysis also considered NO₂ and CO. Hospitalization data were extracted for infants with bronchiolitis diagnoses during the annual respiratory syncytial virus epidemic period (winter) for infants >3 weeks at the time of admission; the purpose of this limitation was to increase the probability of home air pollution exposure after hospital release. Conditional logistic regression models controlled for day of the week, mean daily temperature and humidity. No increased risk of hospitalization for bronchiolitis was found; in some cases, PM_{2.5} even appeared to be protective. However, two positive and significant associations were reported between PM_{2.5} and hospitalization for bronchiolitis in premature infants (25–29 weeks gestation) at lags 3–5 d and 6–8 d with a risk increase of 26% (95% CI 1–57%) and 41% (11–79%) respectively per 10 µg/m³ increase in PM_{2.5}. No dose–response association was observed with increasing gestational age.

Another case-crossover study conducted by Zanobetti and Schwartz (2006) in Boston focused on MI and pneumonia hospital admission in older adults (>65 years). The study used a time-stratified approach and considered BC, PM_{2.5}, CO, NO₂ and O₃ effects in the analysis. BC and PM_{2.5} were found to have some statistically significant associations with hospitalization for pneumonia: excess risks of 11.7% (95% CI 4.8–17.4%) per 1.7 µg/m³ increase in BC and of 3.8% (95% CI 0.64–6.67%) per 10 µg/m³ increase in PM_{2.5}.

Arena et al. (2006) examined the associations between improvements in air quality and cardiopulmonary disease in the older adult population of Alleghany County, PA, from 1995 to 2000 (mean daily average PM₁₀ concentration of 27.9 µg/m³). Day of week, temperature and humidity were treated as potential confounders. During the study period, the authors observed a decrease in cardiopulmonary hospital admissions in the population aged 65–74, but an increase in those ≥75 years old. A decrease in hospital admission rate from 1995 to 2000 was also observed in both African-Americans and whites. There was a seasonal pattern in pulmonary hospital admissions among older adults (greater in the fall and winter); the same pattern was less consistent for cardiovascular events. In addition, the authors reported a significant positive correlation between temperature and PM₁₀, and a significant negative correlation between PM₁₀ and humidity. A positive statistically significant association was also found in unconstrained lag models between current day PM₁₀ levels and hospital admissions. Despite a 17% reduction in PM₁₀ from 1995 to 2000, the health risk associated with PM₁₀ remained, with a 0.61% (95% CI 0.43–0.8%) increase for current day hospital admissions for cardiopulmonary disease per increment of 10 µg/m³ in PM₁₀.

Slaughter et al. (2005) explored the association between various fractions of PM (daily concentrations were 7.9–41.9 µg/m³ for PM₁₀ and 4.2–20.2 µg/m³ for PM_{2.5}) and respiratory (all type, acute asthma and adult COPD) hospital admissions in Spokane, WA. Some positive but non-significant associations were found for different size fractions at different lags. The authors observed an association between CO and emergency room visits (ERVs) for respiratory outcomes, and suggested that these could not reflect direct effects of CO at low environmental concentrations, but rather that CO was acting as a surrogate for PM from combustion sources.

14.5.2.2.3 European studies

Two European multi-city studies are reviewed here. First, in Italy, the results of a fixed effects meta-analysis by Biggeri et al. (2005) revealed that a 10 µg/m³ PM₁₀ increment (mean daily PM₁₀ across cities ranged from 36.5 to 77.6 µg/m³) was associated with an increase in respiratory hospital admissions of 0.73% (95% CI 0.27–1.20%) for lag 0–3 d. When a random effects meta-analysis was conducted, the same PM₁₀ increment was marginally associated with respiratory admissions at the same lag (0.91% (95% CI -0.04–1.86%)). One Bayesian approach

gave a wider confidence interval, but significance remained (0.90% (95% CI -0.18–2.16%) at lag 0–3 d). The overall effect on hospital admissions was slightly modified by the NO₂/PM₁₀ ratio. Another multi-city study was carried out by Eilstein et al. (2004) in nine major French cities. Some statistically significant associations were reported, although no 95% CI were provided. A 10 µg/m³ PM₁₀ increment was associated with respiratory admissions in the aged 0–14 group and in the >65 years group for lag 0–5 d averaged (1.7% and 1.4%, respectively).

Migliaretti and Cavallo (2004) published the results of an Italian case control design study of association between TSP (mean daily average levels of exposure by age group ranged from 105.1 to 114.5 µg/m³) and NO₂ and hospital admissions for asthma in children <15 years of age living in Turin, Italy. Simple and multiple regression models were used with adjustment for season, temperature, humidity, solar radiation, day of the week, holiday, education, gender and age. In single-pollutant models, a 10 µg/m³ TSP increment was associated with a 1.8% (95% CI 0.3–3.02%) increase in hospital admissions for asthma. When modelled with NO₂ this effect became non-significant (0.6% (95% CI -0.2–3.05%)). The authors argued that such results could reflect a confounding effect of NO₂ on the effects of TSP (i.e. that part of the particle effect should be attributed to NO₂).

In Drammen, Norway, Oftedal et al. (2003) conducted a two-step time-series study of respiratory hospital admissions for a 6-year period. This analysis was performed using GAM with log link and Poisson distribution, but some new convergence criteria were used for data treatment and time trend was treated with a cubic spline smoother. Mean daily PM₁₀ concentration was 16.6 µg/m³. The analysis revealed that an increase of 10 µg/m³ in PM₁₀ was associated with an increased risk of 3.17% (95% CI -0.91–7.5%) for respiratory disease hospitalization from 1994 to 1997. For the period from 1998 to 2000, the same increment produced a risk change of -0.72% (95% CI -4.7–3.4%) and for the whole period (1994–2000) the risk change was 1.9% (95% CI -0.91–4.8%).

14.5.2.2.4 Australian studies

Barnett et al. (2005) investigated daily respiratory hospital admissions in five Australian and two New Zealand cities using a case-crossover approach. The following pollutants were considered: PM₁₀, PM_{2.5}, bsp, NO₂, SO₂, O₃ and CO. Mean daily PM₁₀ and PM_{2.5} levels (range across cities) were 16.5–20.6 µg/m³ and 8.1–11 µg/m³, respectively. Analyses were performed for three age groups (0, 1–4 and 5–14 years), with adjustment for long-term trends, seasonal changes and respiratory epidemics, as well as temperature, relative humidity, pressure, temperature extremes, holidays and day of the week. A sensitivity test assessed the influence of each city in the results. In single-pollutant models, many statistically significant results were reported for particulate air pollutants. For pneumonia and acute bronchitis, the highest risk was for fine PM in the 1–4 age group (6.2% (95% CI 0.2–12.1%) per 10 µg/m³ increase in 24-h PM_{2.5}). A 10 µg/m³ increase in 24-h PM_{2.5} was also associated with a 4.4% (95% CI 0.0–8.8%) increase in pneumonia and bronchitis admissions in the 0–12 month age group. In the 0–12 month age group, the same increment in 24-h PM_{2.5} was also associated with a 6.2% (95% CI 2.6–9.8%) increase in respiratory admissions, while in the 1–4 year age group the increase was 4.4% (95% CI 1.8–7.0%). Findings for bsp and for PM₁₀ were generally similar.

In an analysis of multi-pollutant models, Barnett et al. (2005) found that for respiratory admissions in the age 1–4 group (data from four Australian cities only), the effects of PM₁₀ and PM_{2.5} were greater when matched with each other. A 10 µg/m³ increment in 24-h PM_{2.5} averages for the current and previous day was associated with a 4.4% increased risk for respiratory admissions (95% CI 1.8–7.0%) in a single-pollutant model and with a 7.5% increase (95% CI 0.5–14.3%) when matched with PM₁₀, which could reflect separate effects of both fractions. In multi-pollutant models with PM₁₀ or SO₂, the associations with PM_{2.5} remained

positive and (except for pneumonia/bronchitis admissions in the age 1–4 group) statistically significant. For PM_{2.5}, risk estimates for respiratory admissions and for pneumonia and bronchitis admissions were higher in warm than in cool season analyses.

In Australia, Hinwood et al. (2006) used a case-crossover design to study respiratory disease hospitalizations and air pollution in Perth. The air pollutants considered were PM₁₀, PM_{2.5}, CO, NO₂ and O₃. The mean daily concentrations of PM₁₀ and PM_{2.5} were 19.6 and 9.2 µg/m³ respectively. The study focused on CVD, COPD, pneumonia, influenza and asthma, but included gastrointestinal disease as a control disease. Analyses were conducted for all ages, for <15, and for ≥65 years of age. Concentrations of PM_{2.5} were modelled using monitoring station data, a distribution model and interpolation. Conditional logistic regression was used, controlling for temperature and humidity, holidays and weekdays. Seven possible lag period combinations were considered: 0, 1, 2, 3, 0–1, 0–2 and 0–3 d. Some positive associations were found between 24-h PM_{2.5} and pneumonia and respiratory disease hospitalization in the all-age group at lag 3 d. Some significant results were also observed between PM_{2.5} and asthma hospitalization in the all-age group and in the <15 years group at lag 2 d. In the all-ages group, a 10 µg/m³ increase in PM_{2.5} was significantly associated with increases of 2.0% for respiratory disease, 5.1% for pneumonia and 3.0% for asthma hospital admissions; the same PM_{2.5} increment was related to a 5.1% increase for asthma hospitalization in the <15 years (no CI provided).

Erbas and Hyndman (2005) carried out a time-series study in Melbourne for the period from July 1989 to December 1992. The purpose was to explore the association between air pollution and respiratory disease with various statistical approaches and to expose some deficiencies of single-city time-series studies. Asthma and COPD hospital admissions were combined with exposures to UFPs (e.g. PM₁ or PM_{0.1–1.0}), as well as NO₂, SO₂ and O₃. UFPs were measured using equipment that detected back-scattering (B_{scatt}) of light by particle visibility reduction. An air particles index (API) derived from B_{scatt} × 10⁻⁴ was calculated from hourly maximum values from nine fixed ambient air monitors. A seasonal-trend decomposition based on LOESS smoothing was employed to evaluate the strength and magnitude of seasons and variation in pollutants; this method allowed for adjustment of variables with strong seasonal effects. Fourier series were used to measure the seasonality in hospital admissions after seasonality in pollutants and weather variables had been controlled for. Four models were then considered for data analyses: GLM, GAM, a parameter-driven Poisson regression model, and a transitional regression model. A cubic smoothing spline was used for non-parametric functions in the GAM approach. Each model comprised at baseline a temporal time trend, day of the week and seasonal variation function in the outcome variables. A stepwise procedure was used to define the inclusion and functional form of pollutants and weather variables. Temperature (dry bulb) and relative humidity were adjusted for. Instantaneous lags up to 5 d were utilized for data treatment. Using GAM, a negative non-significant association was found between API and COPD admissions (the 10th–90th APIt-2 percentile increase was associated with a reduction in risk of 5% (95% CI -5.0–0%)). While the results for NO₂ remained stable regardless of the model used, the other air pollutants were highly sensitive to model specification. These results suggest that single-city studies should use several models to confirm the stability of the risk estimate that is obtained.

In Brisbane, Australia, the risk of respiratory hospital admissions from bushfire wood smoke pollution has been estimated by Chen et al. (2006) in a time-series study. Three mean PM₁₀ concentration exposure levels were defined for this analysis: <15, 15–20 and >20 µg/m³. Potential confounders (seasonality, day of the week, holidays, long-term trends and influenza) were included when their effect resulted in a ≥10% change in the effect estimate. Three statistically significant (p < 0.01) associations were obtained for current day exposure, the

period for which the strongest effects were observed. For the whole study period, an 11% (95% CI 5–15%) risk increase was calculated for respiratory disease at the 15–20 $\mu\text{g}/\text{m}^3$ PM_{10} exposure level, compared with a 16% (95% CI 10–23%) increase at the >20 $\mu\text{g}/\text{m}^3$ PM_{10} level. When only bushfire occurrence times were considered, a 9% increase for respiratory disease (95% CI 1–18%) was found at the 15–20 $\mu\text{g}/\text{m}^3$ PM_{10} concentrations, compared with a 19% (95% CI 9–30%) increase at the >20 $\mu\text{g}/\text{m}^3$ PM_{10} exposure level. For the non-bushfire period, an increase of 11% for respiratory disease (95% CI 5–17%) was calculated at the 15–20 $\mu\text{g}/\text{m}^3$ PM_{10} exposure, in contrast to the 19% (95% CI 6–23%) increase found at the >20 $\mu\text{g}/\text{m}^3$ PM_{10} concentration level. The overall risk for a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} was 4.0% (95% CI 1.1–6.9%) in the single-pollutant model, but less in a two-pollutant model with ozone (2.6% (95% CI 1.0–5.55%)).

14.5.2.2.5 Other studies

A handful of studies were conducted under conditions that differ widely from Canadian exposures. In Brazil, in a time-series study of the health effects of sugar cane burning, Cançado et al. (2006) investigated respiratory disease hospital admissions in the city of Piracicaba in children (<13 years) and the elderly (>64 years). Some statistically significant results were found between $\text{PM}_{2.5}$ and children's hospital admissions and between PM_{10} and BC and older adult hospital admissions. Some significant associations were observed between industrial emissions and respiratory hospital admissions in the older adults during the non-burning period. Secondly, Lee et al. (2006) conducted a study of the effects of pollution on hospitalizations for asthma among those >18 years old in Hong Kong. In a multi-pollutant model, analyses revealed statistically significant associations between $\text{PM}_{2.5}$ and PM_{10} and asthma admissions at lag 4 d. Third, Tsai et al. (2006b) explored the short-term effect of air pollution on hospital admissions for asthma in Kaoshiung, Taiwan, using a case-crossover design. In a single-pollutant model, several significant associations were found between PM_{10} and asthma admissions on both warm days and cool days. In multi-pollutant models, this effect remained after adjusting for SO_2 , NO_2 and CO. Other significant results were also found with other pollutants. Finally, in Sao Paulo, Brazil, Farhat et al. (2005) conducted a time-series study of the effects of air pollution on respiratory disease ERVs due to lower respiratory tract disease and on hospital admissions of children for pneumonia or bronchopneumonia combined or for asthma and bronchiolitis combined. In single-pollutant models, PM_{10} was associated with increased hospital admissions for pneumonia/bronchopneumonia, and for asthma/bronchiolitis, though the latter result was non-significant. In two-pollutant models, an IQR increase in PM_{10} over a 5-d moving average was associated with an increased risk of pneumonia/bronchopneumonia hospital admissions when modelled with NO_2 , SO_2 , O_3 and CO, though only O_3 and CO remained significant. For asthma/bronchiolitis hospital admissions, no significant associations with PM_{10} remained. In the multi-pollutant model, which included all five pollutants, none of them was significantly associated with an increase in hospital admissions for pneumonia/bronchopneumonia, or for asthma/bronchiolitis.

14.5.2.3 Cardiovascular Admissions

A total of 30 studies originating from North America (16), Europe (6), Australia (1) and Asia (7) have been reviewed. The majority (17 studies) were time-series in design, while 12 case-crossover studies were identified. The most common PM metric was PM_{10} ($n = 28$); only seven studies used $\text{PM}_{2.5}$ for analysis, while BS was used in two European studies.

14.5.2.3.1 Canadian studies

Two single-city Canadian studies were conducted by Fung and collaborators. In a time-series study (Fung et al., 2005a) of cardiac disease hospital admissions in Windsor, ON, between 1995 and 2000, pollutant data (PM_{10} , COH, SO_2 , CO, NO_2 and O_3) were collected from four

fixed ambient air monitoring stations (mean daily high concentration was $50.6 \mu\text{g}/\text{m}^3$). Subjects were stratified by age (< or ≥ 65 years) and current-day, 2-d average and 3-d average lags were explored. GLMs were used to account for meteorological, seasonal and weekly cycles. No significant associations were observed between PM_{10} and cardiac disease hospital admissions; however, a positive non-significant association was observed in subjects <65 years of age for a 3-d average, with a change of 0.48% (95% CI -1.04–2.2%) for a $10 \mu\text{g}/\text{m}^3$ PM_{10} increment. Positive effects were also associated with COH and cardiac disease hospital admissions in the <65 group at lag 0 d, with a 1.6% (95% CI -3.8–7.3%) increased risk per 0.5 COH IQR. The second study (Fung et al., 2005b) was of a very similar design (mean maximum daily level was $38 \mu\text{g}/\text{m}^3$), although only lags 0–2 d were explored. In this study cardiovascular and respiratory hospital admissions were studied in London, ON. Significant effects were associated with COH, which was linked to cardiac disease hospital admissions in the <65 group at lag 0 d, (5.7% increase (95% CI 0.9–10.8%) per 0.7 COH IQR); the older adult group revealed a positive non-statistically significant association with a 2.1% increase (95% CI -2.3–4.2%). PM_{10} was also non-significantly associated with cardiac disease hospital admissions in individuals <65 years of age (a 0.99% increase (95% CI -0.9–2.9%) per $10 \mu\text{g}/\text{m}^3$ increase).

14.5.2.3.2 US studies

Several US multi-city studies were identified. As mentioned in Section 14.5.2.2.2, Dominici et al. (2006) conducted a large time-series study that examined hospital admissions for cardiovascular and respiratory disease in older adults. The highest cardiovascular effect for a $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ increase was 1.28% (95% CI 0.78–1.78%) for risk of admission for CHF in the Medicare group >65 years of age at lag 0 d; an increase of 1.36% (95% CI 0.78–1.94%) was also reported for CHF admission in the ≥ 75 group at lag 0 d. The strongest effect on IHD hospitalizations was observed in the ≥ 75 group at lag 2 d, with a 0.52% risk increase (95% CI -0.01–1.04%). Effects on cardiovascular admissions were stronger in the eastern US; risk estimates for these outcomes were positive in the east, but not in the west. These results are similar to those reported by Fuentes et al. (2006) and Franklin et al. (2007), who found greater risks for cardiovascular mortality in the eastern US (see Section 14.5.1.2.2). Each $10 \mu\text{g}/\text{m}^3$ reduction in daily $\text{PM}_{2.5}$ was associated with annual reductions in hospital admissions ranging from 602 (95% PI -42–254) for peripheral vascular disease to 3156 (95% PI 1923–4389) for CHF. In addition, this team assessed the effects of air pollution on cardiovascular hospitalizations in older adults using a time-series design with data from 10 American cities taken from the NMMAPS database for 1986–1993 (Dominici et al., 2004). An increased risk of 0.71% (95% CI 0.35–0.99%) for cardiovascular-related hospital admissions was associated with each $10 \mu\text{g}/\text{m}^3$ PM_{10} increment in the current and previous day averages.

Wellenius et al. (2005b) investigated the associations between pollution and hospital admissions for ischemic and hemorrhagic stroke in older adult Medicare beneficiaries in nine US cities from 1986 to 1999, using a two-stage hierarchical model. Daily mean air pollution values were obtained from the US EPA monitoring network (median PM_{10} was $28.36 \mu\text{g}/\text{m}^3$), excluding days with PM_{10} levels greater than $150 \mu\text{g}/\text{m}^3$, which is the current 24-h US EPA standard. A $10 \mu\text{g}/\text{m}^3$ PM_{10} increment was associated with a 0.45% (95% CI 0.02–0.88%) increase in risk for ischemic stroke admissions at lag 0 d. No significant results were observed for hemorrhagic stroke admissions. The same group also examined the association between air pollution and CHF hospital admissions in the older adult populations of seven US cities during 1986–1999 using the same pollutant data and a similar study design (Wellenius et al., 2006). Lags of 0–3 d were explored; the specific study design controlled for seasonality, time trends and other chronic or slowly varying confounders. Age, gender, race and many specific secondary diagnoses were treated as potential effect modifiers. This study revealed a positive association between PM_{10} and same-day CHF admissions in six cities (a negative non-

significant association was observed for the seventh city). A statistically significant effect on CHF admissions in Medicare recipients ≥ 65 years was found in the overall all-cities analysis (0.72 % (95% CI 0.35–1.10%) per 10 $\mu\text{g}/\text{m}^3$ PM_{10} increase; $p = 0.0002$). No evidence of heterogeneity was observed between cities and no evidence of effect modification was associated with patient secondary diagnosis.

Zanobetti and Schwartz (2005) reported the results of a case-crossover study that was conducted in 21 cities and focused on MIs in the older adult population. This research revealed an increased risk of 0.65% (95% CI 0.1–1.2%) in hospital admissions for MI for each 10 $\mu\text{g}/\text{m}^3$ increment of PM_{10} ; matching on apparent temperature yielded an estimate of 0.64% (95% CI 0.1–1.2%). The shape of the concentration–response curve was investigated by fitting a piecewise linear spline with slope changes at 20 and 50 $\mu\text{g}/\text{m}^3$, which resulted in an almost linear relationship, with little or no indication of a threshold. An important but non-significant effect on MI hospital admissions was observed for acute or chronic lower respiratory disease. A 1.3% (95% CI -0.1–2.85%) increased risk of hospitalization for MI was noted in subjects with previous admissions for COPD, compared with a 0.6% (95% CI 0.3–1%) increase for subjects without such previous admissions. An increased risk of 1.4% (95% CI -0.8–3.6%) in hospitalization for MI in subjects with previous admissions for secondary diagnosis of pneumonia was also reported, compared with a 0.6% (95% CI 0.3–1%) increase for subjects without this diagnosis. No other effect modifier showed positive results, except for gender (males, 0.9% (95% CI 0.2–1.60%); females, 0.5% (95% CI 0.05–1.97%)). The results from this study showed an important association between PM and emergency MI hospitalization at lag 0 d, suggesting that exposure to PM may trigger an MI.

Several single-city studies have also explored the possible associations between PM and cardiovascular hospitalizations. A time-series study by Arena et al. (2006) examined the effect of air pollution on cardiopulmonary disease in the older adult population of Allegheny County, PA (mean daily average PM_{10} concentration of 27.9 $\mu\text{g}/\text{m}^3$). This study revealed a statistically significant association between a 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} and hospitalization for cardiopulmonary disease at lag 0 d, with an excess risk of 0.61% (95% CI 0.43–0.8%). In New York City, Low et al. (2006) conducted a time-series study that explored the association between stroke and some specific factors that could be related to stroke, such as air pollutants (pollen, O_3 , SO_2 , NO_2 , NO_x , CO and PM_{10}), upper respiratory disease (URD) and asthma visits using autoregression with 365-d lags. The mean daily concentration of PM_{10} was 23.56 $\mu\text{g}/\text{m}^3$, and visits for rehabilitation were excluded from the analysis. The influence of seasons, day of the week, major holidays and September 11th were also examined. In a multivariate analysis, an increase of 1 $\mu\text{g}/\text{m}^3$ PM_{10} was associated with an additional 0.008 admissions for ischemic stroke or stroke of undetermined origin (broad stroke definition), with $p = 0.0404$. Considering the PM_{10} maximum concentration reported in this study (89.53 $\mu\text{g}/\text{m}^3$), this was estimated to be associated with 0.677 stroke episodes per day. URD also produced a significant independent effect on broadly defined stroke (coefficient, 0.00083; SE, 0.00018; $p < 0.0001$), as did air temperature, dry air, grass pollen and SO_2 .

Another time-series study was carried out by Mann et al. (2002) in California's South Coast Air Basin; it investigated the effects of air pollution on IHD in those having CHF or arrhythmia. The subjects were members of Southern California's Kaiser Permanente (a non-profit health care organization) and resided within 20 km of one of five PM monitoring stations used in a 1995 intensive PM monitoring campaign. Hourly (O_3 , NO_2 , and CO) and 6-d (PM_{10}) data were also collected (mean daily PM_{10} concentration of 43.7 $\mu\text{g}/\text{m}^3$). Ozone and PM_{10} frequently exceeded national air quality standards; 25% of the time, PM_{10} concentrations were higher than 50 $\mu\text{g}/\text{m}^3$. The health outcomes investigated were IHD admission with no secondary diagnosis, IHD with CHF, and IHD with arrhythmia. To evaluate the potential effect of age, results were stratified

based on age (40–59 and ≥ 60). The annual rate of IHD admissions was 10-fold greater in the older age group (29.9/1000 vs. 2.5/1000) and similar results were observed for specific IHD diagnoses. No significant association was found between PM_{10} and IHD admission at any lag or moving average. While significant associations between CO and NO_2 and IHD admissions were found, only small positive associations were observed for PM_{10} , with 0.59% (95% CI -0.71–1.91%) and 0.46% (95% CI -0.86–1.80%) IHD admission increases per $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} , with lags 0 and 1 d respectively.

In Spokane, WA, Slaughter et al. (2005) assessed the effect of exposure to air pollution on respiratory and cardiac disease hospital admissions in adults (mean daily concentrations ranged from 7.9 to $41.9 \mu\text{g}/\text{m}^3$). Season, temperature and relative humidity as well as day of the week were controlled for. Some positive non-significant associations were found with various air pollutants using different lag structures. Stronger associations were generally observed for $PM_{2.5}$ than for PM_{10} . However, the lack of consistency between PM size fractions, health outcomes and lag structures limits the conclusions that can be drawn from this research. Another time-series study on the effects of air pollution in older adults was conducted in Denver County, CO, by Koken et al. (2003), who assessed the impact of summer air pollution and temperature on daily hospital admissions for CVD in individuals >65 years old. A normalizing factor was included in the GLM to account for population variation over the study period. No significant associations were observed between CVD hospital admissions and PM_{10} (data not shown).

Five case-crossover studies were identified in the recent literature; however, each investigated a different endpoint. In a case-crossover study of hospital admissions for MI in older adults that was conducted in Boston, MA, using a time-stratified approach, Zanobetti and Schwartz (2006) found an association with an increment of $10 \mu\text{g}/\text{m}^3$ in $PM_{2.5}$ at lag 0 d (4.87% (95% CI 1.10–8.17%) and at 0–1 d lagged average (5.2% (95% CI 0.73–9.17%)). A significant association was also observed with BC for 0–1 d averaged lag (60.2% (95% CI 18–137%) per $10 \mu\text{g}/\text{m}^3$ increase in BC). Statistically significant associations were reported with other pollutants (CO, NO_2 , and O_3). Also in the US, Symons et al. (2006) conducted a case-crossover study of the risk for onset of symptoms leading to CHF admissions at Baltimore's Johns Hopkins Bayview Hospital through the emergency department. Interview-administered questionnaires were used to gather information on the time of onset of symptoms (TOS). Sampling of $PM_{2.5}$ occurred at hourly, daily and 3-d intervals (mean 8-h and 24-h average $PM_{2.5}$ concentrations of 17 and $16 \mu\text{g}/\text{m}^3$, respectively), and CO, NO_2 and O_3 were also measured. A time-stratified approach was used to control for time factors and to remove potential overlap bias; an adjustment was made for temperature and humidity. In a single-pollutant model, a $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ was associated with a 7.38% (95% CI -7.5–24.2%) increase for 8-h TOS cases at lag 2 d. In two-pollutant models a trend was also observed in 8-h TOS cases of CHF with $PM_{2.5}$ increments (increased risk of 7.38% (95% CI 7.5–24.1%), 2.47% (95% CI -11.72–20.25%) and 3.29% (95% CI -12.57–21.84%) after adjusting for O_3 , CO and NO_2 respectively). Such effects were not found for 24-h TOS cases. Moreover, some positive associations were also reported for other pollutants and in single-pollutant models, a significant association was reported between CO and 8-h TOS cases at lag 2 d. The authors suggested that better definitions of case and exposure timing were among the strengths of this study, while the weaknesses included use of $PM_{2.5}$ from ambient air monitors (even if other similar studies revealed that personal and ambient $PM_{2.5}$ are highly correlated) and imprecision in TOS identification for some participants, which may have affected the ability to accurately estimate the risk of hospitalization.

Finally, Wellenius et al. (2005a) assessed the association between air pollution and hospitalizations for CHF in the older adult population of Pittsburgh, PA, using a time-stratified case-crossover design. Potential effect modification was examined for age, gender and many

cardiorespiratory diagnoses. The linearity of the concentration–response curve fitted using fractional polynomials and linear splines was examined, and the authors reported that the assumption of linearity was reasonable. The mean daily PM₁₀ concentration was 31.06 µg/m³. In single-pollutant models, a 10 µg/m³ increase in PM₁₀ was associated with an increased CHF hospital admission rate of 1.27% (95% CI 0.66–1.88%). In a two-pollutant model with CO, PM₁₀ was negatively associated with hospitalizations for CHF (-0.46% (95% CI -1.27–0.36%)). By contrast, positive associations were observed in two-pollutant models with NO₂ (0.22% (95% CI -0.61–1.05%)), ozone (1.16% (95% CI 0.54–1.66%)) and SO₂ (0.98% (95% CI 0.15–4.02%)). The effect of PM₁₀ was more than 3-fold greater in patients with a secondary diagnosis of MI within the past 30 days than in those without a recent MI diagnosis.

In western Washington State, Sullivan et al. (2003) explored the association between air pollution and primary cardiac arrest in subjects with or without pre-existing cardiac conditions. They used a case-crossover approach and ORs were calculated using conditional logistic regression models. Mean daily PM₁₀ concentrations for lag 0, 1, and 2 d were 28.05, 27.97, and 28.4 µg/m³, respectively. Primary cardiac arrest was not associated with PM in univariate analyses; significant associations in analyses stratified by disease state were, however, observed at lag 2 d in subjects who smoked. A 13.8 µg/m³ increment of PM_{2.5} was associated with cardiac arrest in all subjects with supraventricular tachycardia (OR = 1.55 (95% CI 1.07–2.25) at lag 1 d) and in current smoker subjects with supraventricular tachycardia (OR = 12.80 (95% CI 1.05–156.57) the day of the event). In addition, the risk of primary cardiac arrest was significant in subjects who smoked, had heart disease and did not use cardiac medications as compared with those using these medications. The research group also investigated the existing associations between PM and MI in 69 adults from King County, WA (Sullivan et al., 2005a). This additional case-crossover study revealed no significant associations between PM_{2.5} and the onset of MI in either the main analysis or when data were stratified by cardiovascular risk factors or season (mean PM_{2.5} and PM₁₀ levels of 12.8 and 28.3 µg/m³, respectively), though the risk estimate for fine PM was non-significantly increased in persons with previous CHF, previous MI, or diabetes. In addition, no significant associations were observed with other pollutants (CO and SO₂).

14.5.2.3.3 European studies

Six European multi-city studies focused on cardiovascular hospital admissions. In Spain, Ballester et al. (2006) carried out a time-series study of cardiovascular and heart disease hospital admissions associated with air pollution (PM₁₀, BS, TSP, SO₂, NO₂, CO and O₃) in 14 cities. Pollutant measurements were obtained from city monitoring networks (mean daily PM₁₀ and TSP concentrations ranged from 35.7 to 43.2 µg/m³ and from 51.8 to 77.4 µg/m³, respectively). Influenza epidemics, temperature, relative humidity and barometric pressure, day of the week and holidays and unusual events (ex: medical strike) were controlled for. Single- and two-pollutant models were performed. In preliminary analyses, the linearity of the concentration–response relation was examined in either a linear or non-linear way (with a spline smoothing function); the authors reported that the shape of the relation was compatible with a linear one in most cases. A 10 µg/m³ increase in PM₁₀ was associated with an increased risk of both CVD hospital admissions at lag 0–1 d (0.91% (95% CI 0.35–1.47%)) and heart disease hospital admissions (1.56% (95% CI 0.82–2.31%)). A 10 µg/m³ increment in BS was also associated with cardiovascular and heart disease hospital admissions (0.24% (95% CI -0.18–0.67%) and 0.71% (95% CI 0.13–1.29%), respectively). Similar associations with an increase of 10 µg/m³ in TSP were also observed (0.07% (95% CI -0.23–0.36%) and 0.45% (95% CI 0.04–0.86%) for CVD and heart disease hospital admissions, respectively). In two-pollutant models the associations with PM₁₀ remained significant when matched with all other pollutants (no data provided, graphics only). The PM₁₀-associated estimate was more attenuated when combined

with SO₂ but the association remained significant. In Italy, Biggeri et al. (2005) reported positive results from a multi-city study (mean daily average PM₁₀ ranged from 36.5 to 77.6 µg/m³). For lag 0–3 d, a 10 µg/m³ PM₁₀ increment was significantly associated with cardiovascular hospital admissions, with an excess risk of 0.77% (95% CI 0.40–1.15%) in a fixed effects model and of 0.82% (95% CI 0.32–1.32%) in a random effects model. Using a Bayesian approach gave wider confidence intervals, but significance was preserved with a 0.81% increased risk (95% CI 0.32–1.38%) at lag 0–3 d for cardiovascular hospital admissions. The overall effect on hospital admissions was slightly modified by the NO₂/PM₁₀ ratio.

In France, Eilstein et al. (2004) conducted a time-series study focused on hospital admissions for cardiovascular and respiratory disorders in nine French cities. Some positive non-statistically significant associations were found between a 10 µg/m³ increment of PM₁₀ and cardiovascular outcomes in the >65 age group (0.1% at 0–1 d lag, and 0.7% for average 0–5 d lag (no 95% CI provided)). Lanki et al. (2006a) conducted a study of first acute MI hospitalization in adults aged >35 years (35–74 years in Augsburg, Germany, 35–79 in Barcelona, Spain) from five major European cities. PM₁₀, UFPs, CO, NO₂ and O₃ were collected from fixed ambient monitors. Time trend, average apparent temperature, day of the week and holidays were included in the model. Age, fatality and season were assessed as possible effect modifiers, with fatality stratified analysis restricted to data from three cities with hospital discharge registers (HDRs): Helsinki, Finland, Rome, Italy, and Stockholm, Sweden. The sensitivity of the results to temperature was evaluated with 1–3 d lagged average temperature. An alternate approach for smoothing was assessed with natural spline in GLM. The effects of days with high pollution levels were also assessed by considering the days with <98th percentile air pollutant concentrations. In cities with HDRs, a borderline association was found for UFPs at lag 0 d (a 1.3% increased risk for acute MI (95% CI 0–2.6%) per 10,000 particles cm⁻³). A further analysis in cities with HDRs also revealed a marginal association in the <75 age group, with a 3.1% excess risk for fatal acute MI (95% CI 0–6.4%) per 10 µg/m³ increase in PM₁₀ on same-day lag and 5.0% (95% CI 0–10.1%) per 10,000 particles cm⁻³ PNC, also on same-day lag. The PNC risk increased to 3.2% for a non-fatal acute MI (95% CI 0.8–5.6%) in the >75 age group. A greater effect was seen for PNC during the warm season (5.0% for non-fatal AMI (95% CI 1.6–8.5%)) at lag 2 d. Some other positive but non-significant associations were found for PM₁₀ and PNC with various lag and group conditions.

Von Klot et al. (2005) conducted a multi-city cohort study in five European cities (mean daily PM₁₀ range across cities was 14.6–52.2 µg/m³). Hospital readmissions were assessed in a cohort >35 years of age who had survived a first MI. Associations between MI, angina pectoris and cardiac causes (including MI, angina pectoris, dysrhythmia and CHF) and air pollutants (PM₁₀, UFP, CO, NO₂ and O₃) were investigated. Potential confounders were controlled for, including long-term trends, seasonality, changes in baseline rate, day of the week and vacations, meteorology and change in temperature over the previous three days. The analysis of the results revealed that a 10 µg/m³ PM₁₀ increase was associated with an increased risk of 2.1% for cardiac readmissions (95% CI 0.4–3.9%) at lag 0 d, with a similar effect for a 10,000 particle cm⁻³ increase in PNC (2.6% (95% CI 0.5–1.048)). The only city-specific significant result was for PNC in Augsburg, Germany, at lag 0 d (data not provided, graphic only); however, city-specific results were statistically homogenous. In two-pollutant models, the effect of PNC remained stable when controlling for PM₁₀ or ozone, but the existing association between readmissions and PM₁₀ was weakened (data not provided).

The relationship between air pollution and first MI hospital admission in Rome, Italy, was assessed by D'Ippoliti et al. (2003) using a time-stratified case-crossover analysis. TSP, SO₂, NO₂ and CO were considered in analyses using conditional logistic regression and models adjusted for temperature and humidity (mean daily all-year TSP concentration of 66.9 µg/m³).

Potential effect modification by age, gender, season and specific adverse health conditions was investigated. The strongest association was observed between exposure to TSP and risk of MI, with a consistent trend observed with increasing TSP concentration. In a single-pollutant model, a 10 $\mu\text{g}/\text{m}^3$ increment in TSP was associated with a 2.8% risk increase (95% CI 0.5–5.2%) for acute MI hospital admission at lag 0–2 d. This was slightly reduced in two-pollutant models: a 2.5% increase (95% CI 2.2–7.5%) with TSP and CO and a 1.3% increase (95% CI 0.1–4.6%) with TSP and NO_2 . Higher risk estimates were reported in women (excess risk of 3.9% (95% CI 0–8.0%)), in the warm season (4.6% (95% CI 0.8–8.7%)), in older adults (4.6% (95% CI 0.5–8.9%)) and in individuals with heart conduction disorders 8.0% (95% CI -1.3–18.1%). No significant effects were found in individuals with diabetes or hypertension.

14.5.2.3.4 Australian studies

Barnett et al. (2005) conducted a time-stratified case-crossover investigation of the effects of PM_{10} , $\text{PM}_{2.5}$, NO_2 , CO and O_3 on daily hospital admission for CVD in residents of five Australian and two New Zealand cities, stratified by age (15–64 and ≥ 65 years). Daily measurement was made for all pollutants; $\text{PM}_{2.5}$ was measured daily in four cities (mean daily level 8.1–11 $\mu\text{g}/\text{m}^3$), while PM_{10} was measured in five cities (mean daily level 16.5–20.6 $\mu\text{g}/\text{m}^3$). Long-term trends, seasonal changes and respiratory epidemics were controlled by design; additional controls were made for temperature, relative humidity, pressure, temperature extremes, day of the week and holidays, and in some cases rainfall. A random effects meta-analysis was used to assess the average all-cities effect. A hierarchical model was used to investigate differences between cities using various effect modifiers. Each city's hospital admission increase was regressed against potential effect modifiers such as air pollution level, percentage of older adult population or temperature. A 10 $\mu\text{g}/\text{m}^3$ increment in $\text{PM}_{2.5}$ was associated with statistically significant increases in hospital admissions among persons ≥ 65 years old: 5.08% (95% CI 2.65–7.26%) for cardiac diseases, 9.75% (95% CI 4.81–14.84%) for cardiac failure, 4.27% (95% CI 1.85–6.44%) for IHD, 7.3% (95% CI 3.5–11.4%) for MI and 3.36% (95% CI 1.59–5.35%) for total CVD. For PM_{10} , a 10 $\mu\text{g}/\text{m}^3$ increment was also associated with significant increases in hospital admissions for those ≥ 65 : 1.47% (95% CI 0.27–2.68%) for cardiac diseases and 4.56% (95% CI 2.81–6.32%) for cardiac failure. Higher risks were also observed in the older adults in association with exposure to CO and NO_2 . A greater association was found for arrhythmia in the 15–64 age group (data not presented). No association was observed between exposure to air pollution and stroke in either age category. Significant effect modifiers were observed only for $\text{PM}_{2.5}$; stronger associations were seen with cardiac admissions in cities with lower humidity and an association with cardiac failure was found in cities with higher atmospheric pressure and a higher proportion of older adults.

Hinwood et al. (2006) used a case-crossover design to study respiratory and CVD hospitalizations and air pollution in Perth (mean daily concentrations of PM_{10} and $\text{PM}_{2.5}$ were 19.6 and 9.2 $\mu\text{g}/\text{m}^3$, respectively). Some positive results were observed between 24-h $\text{PM}_{2.5}$ and respiratory disease and pneumonia hospitalizations; however, this study found no association between pollutants and CVD hospital admissions.

14.5.2.3.5 Other studies

Seven CVD hospital admission studies were conducted in other countries with environments dissimilar to Canadian exposures. Three were carried out in Taipei, Taiwan. Chang et al. (2005a) used a case-crossover approach to assess the effects of air pollution on CVD hospital admissions. In a single-pollutant model, a significant association was found between CVD admissions and all pollutants except SO_2 ; the effect of PM_{10} was observed on both warm ($>20^\circ\text{C}$) and cool ($<20^\circ\text{C}$) days. In two-pollutant models, the effect of PM remained significant after including SO_2 and O_3 for warm days and significant in all two-pollutant models for cool

days. Chan et al. (2006) carried out a time-series study of the association between air pollution and daily ERVs for cerebrovascular disease, stroke, hemorrhagic and ischemic stroke in the population >50 years of age. Statistically significant associations were found for PM_{2.5} in a single-pollutant model, but not in two- and three-pollutant models. The effects of CO and O₃ on cerebrovascular admissions were greater than for PM or NO₂. Yang CY et al. (2005) investigated the effects of Asian dust storm events on daily stroke hospital admissions and found a significant association with daily hospital admissions for primary intracerebral hemorrhagic stroke 3 d later. Similar associations for total stroke admissions and ischemic stroke were marginally significant. In another Taiwanese case-crossover study, Tsai et al. (2003b) investigated hospital admissions for stroke; on warm days (>20°C) PM₁₀ was significantly associated with primary intracerebral haemorrhage and with ischemic stroke admissions. Comparable results were obtained in multi-pollutant models. In Seoul, South Korea, a time-series study conducted by Lee JT et al. (2003) on hospital admissions revealed a significant association between PM₁₀ and IHD hospital admissions in older adults at lag 5 d. This association was marginally significant when considering only the summer months. In two-pollutant models, the effect of PM₁₀ remained with the individual inclusion of all gaseous pollutants except NO₂. In a single-pollutant model, PM₁₀ was also significantly associated with CVD hospital admissions for both cool and warm days in a case-crossover study in Kaoshiung, Taiwan (Yang et al., 2004b). In two-pollutant models, on warm days, PM₁₀ remained significant when SO₂, NO₂ or CO were included; on cool days, PM₁₀ remained significant with SO₂, CO and O₃. In Tehran, Iran, a retrospective time-series study by Hosseinpour et al. (2005) revealed a nearly significant association between hospital admissions for angina pectoris and PM₁₀ at lag 1 d; in a multi-pollutant model, this relationship was not significant.

14.5.2.4 Summary and Considerations: Hospital Admissions

Continuing the findings summarized in the US EPA 2004 PM AQCD, virtually all of the studies reviewed in this assessment reported positive associations between ambient PM and hospital admissions for various respiratory and cardiovascular conditions. With the exception of some of the single-city studies, these associations were all statistically significant. Positive findings were reported for various environmental conditions, using different analytical approaches (e.g. time-series, case-crossover) and PM metrics. While PM₁₀ was the most frequently studied size fraction, significant associations with respiratory or cardiovascular hospitalizations were also reported for PM_{2.5}, BS, TSP, PM_{10-2.5} and COH, though the number of studies with the latter three fractions was limited. The single-pollutant effect estimates from the multi-city studies with PM₁₀ ranged from 0.3% to 2.54% for hospitalizations for various respiratory endpoints, and from -0.25% to 4.56% for cardiovascular hospitalizations (figures 14.19 and 14.20). The corresponding values for PM_{2.5} ranged from 0.91% to 6.44 % and from 1.28% to 9.75%, respectively (figures 14.21 and 14.22). Associations between ambient PM and hospital admissions generally did not display marked seasonality, with seasonally restricted analyses providing results similar to those for the full year.

The possible role of co-pollutants in PM-related associations with hospital admissions was examined in a minority of the reviewed studies. In most of these, the association with PM remained positive and statistically significant in multi-pollutant analyses with one or more of SO₂, NO₂, CO or O₃. There was some indication in these studies that PM-related effects are more robust in models with O₃ (with which PM is often not strongly correlated), and least robust in those with NO₂ (with which the correlation is often relatively strong).

Figure 14.19 Risk estimates for respiratory hospitalization per 10 µg/m³ increase in PM₁₀ concentration in single-pollutant models

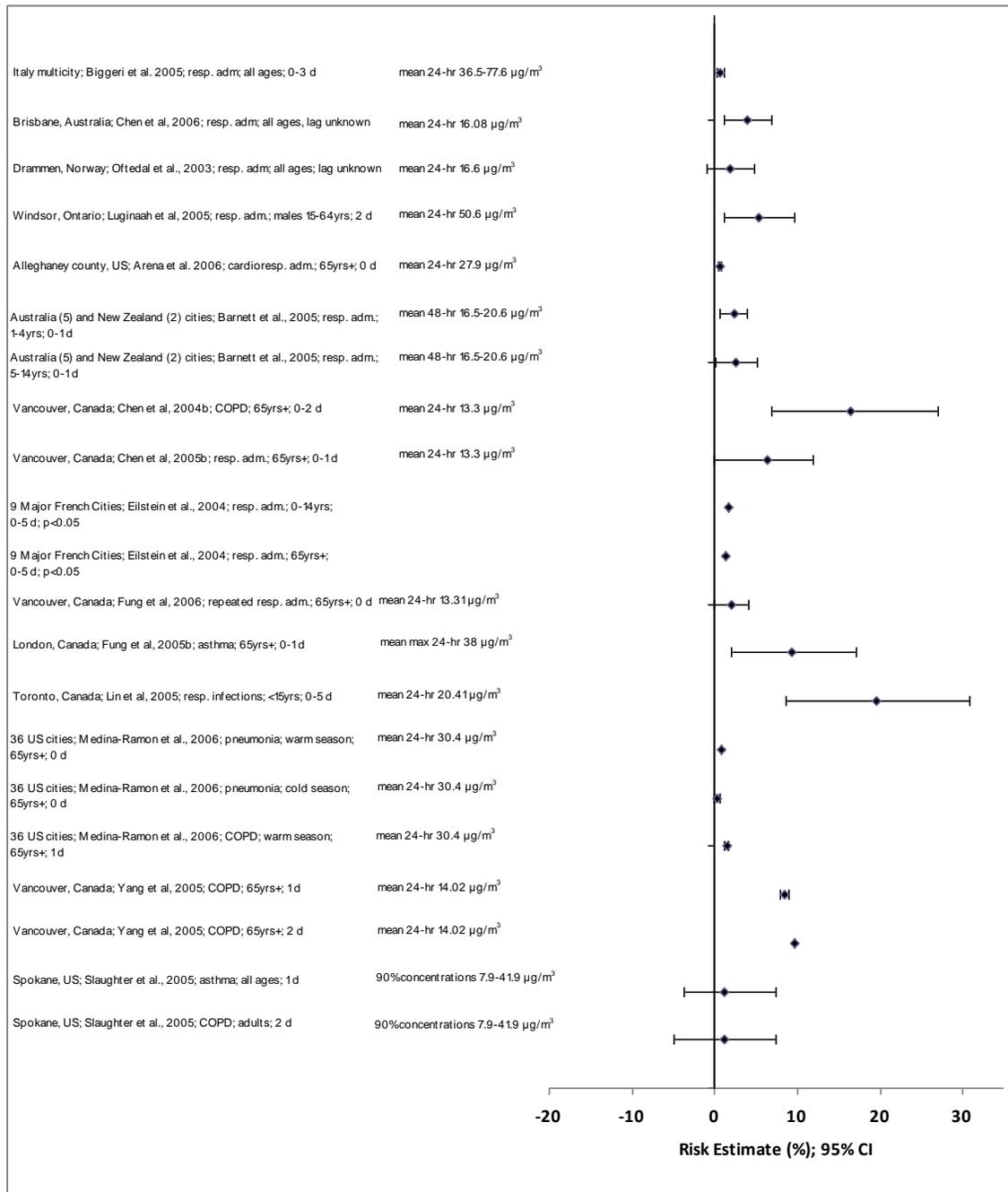


Figure 14.20 Risk estimates for cardiovascular hospitalization per 10 µg/m³ increase in PM₁₀ concentration in single-pollutant models

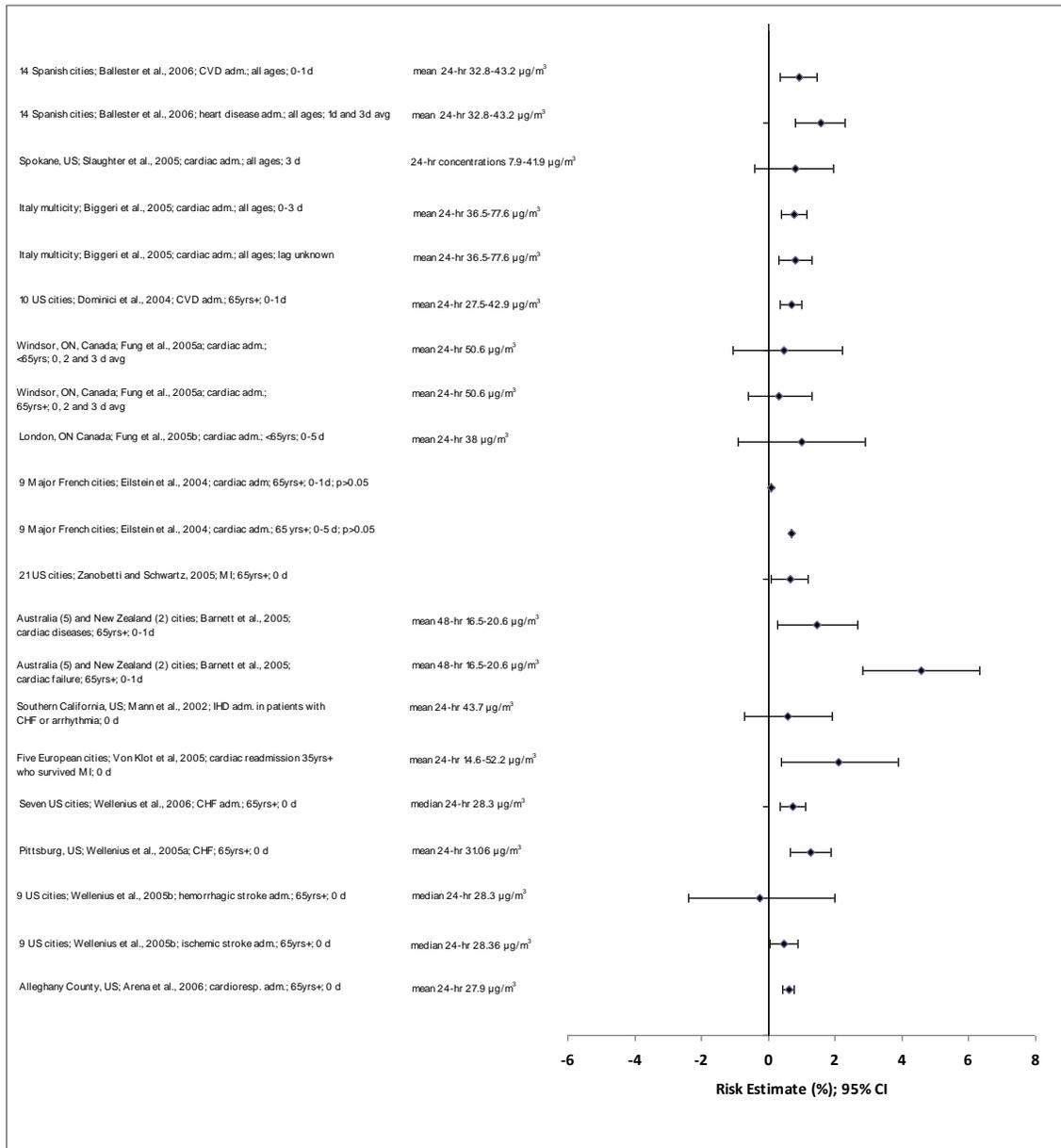


Figure 14.21 Risk estimates for respiratory hospitalization per 10 µg/m³ increase in PM_{2.5} concentration in single-pollutant models

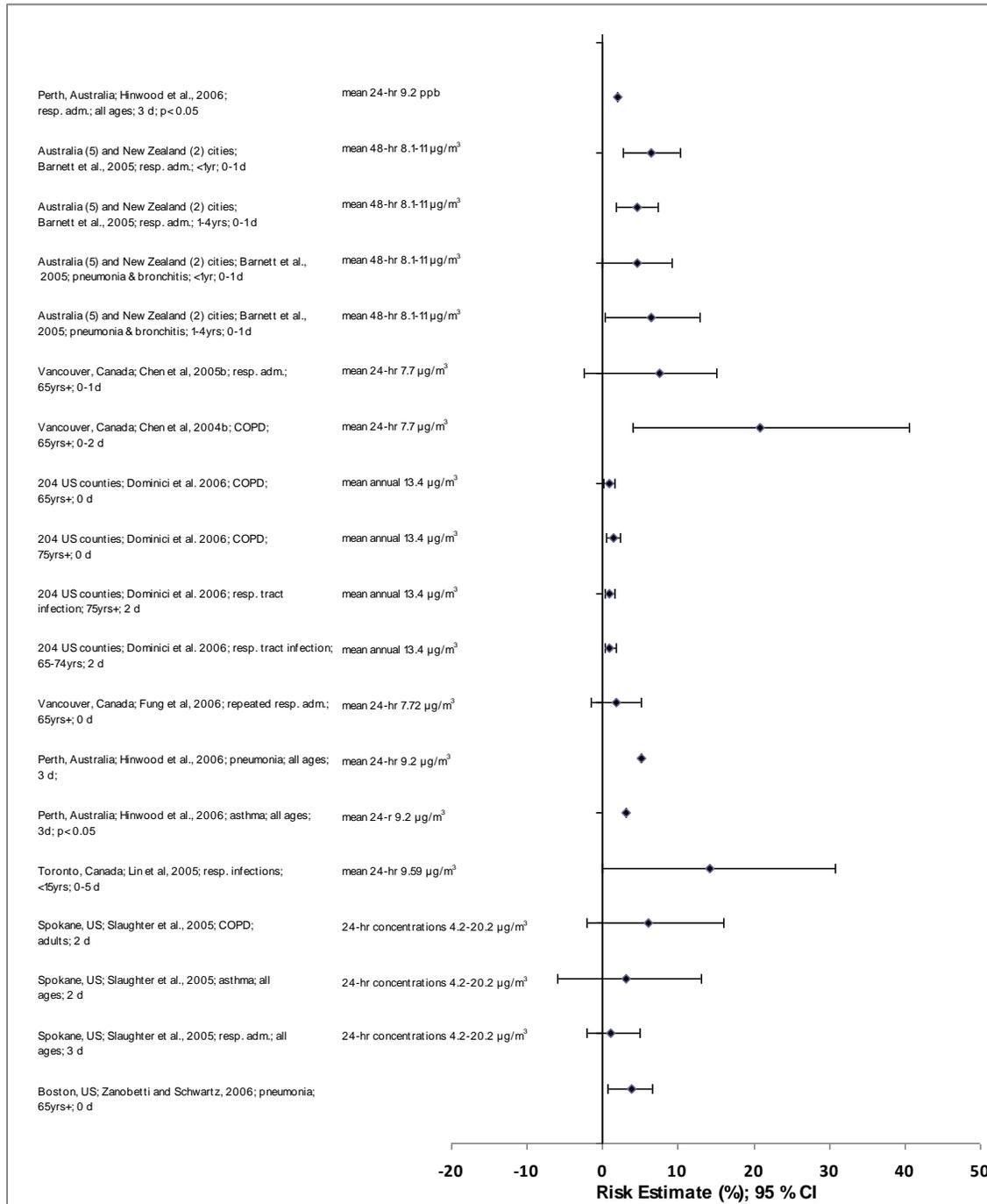
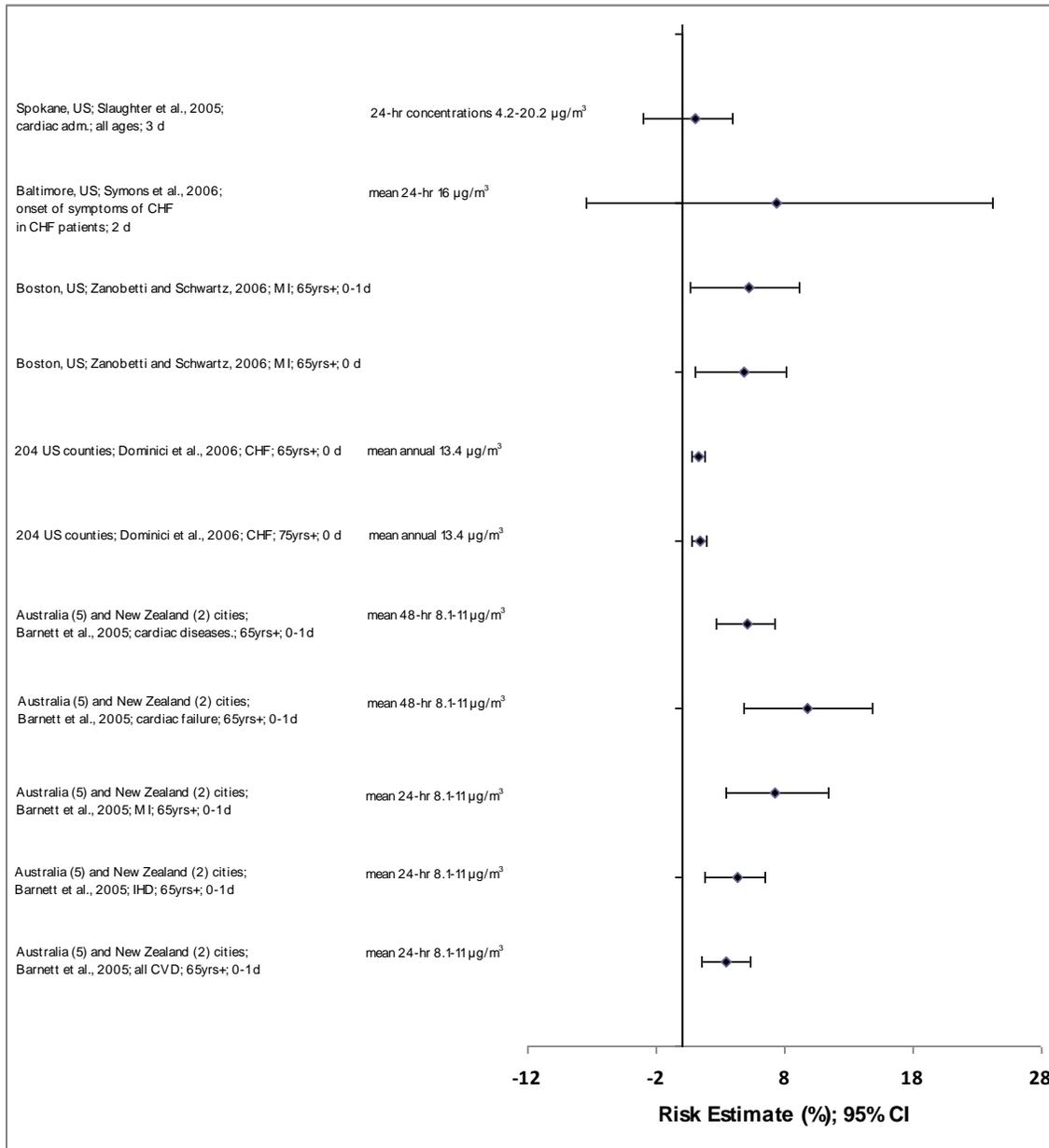


Figure 14.22 Risk estimates for cardiovascular hospitalization per 10 µg/m³ increase in PM_{2.5} concentration in single-pollutant models



There are fewer examples of this type of study than are found for premature mortality, largely because centralized databases of hospital admissions are far less common and there are challenges in using the data. Because the statistical power (i.e. sample size) in these studies tends to be less than for premature mortality, there is less opportunity to segregate specific causes; however, in studies large enough for specific analysis, the risk estimate and level of statistical significance were greater for specific disease categories, indicating that people with these conditions are more susceptible to the health effects of air pollution. For respiratory conditions, susceptible populations consistently included those with asthma (especially children) and/or other COPD, whereas for cardiovascular conditions newer studies highlighted those with various heart conditions, as well as investigating more specific outcomes (e.g. ischemic stroke vs. hemorrhagic stroke; fatal and non-fatal MIs, CHF or IHD with or without prior diagnoses). Risks were often greatest in adults and the elderly, perhaps because cardiorespiratory disease is far more prevalent after the age of 55, though many of the studies reviewed did not examine younger age classes in any detail, instead focusing on older individuals.

Only a small number of recent Canadian studies, all conducted in single cities, were identified in this review (Chen et al., 2004b, 2005b; Fung et al., 2005a, 2005b, 2006; Lin et al., 2005; Luginaah et al., 2005; Yang et al., 2005). The results of these studies are generally consistent with those from elsewhere, many of which have revealed associations at ambient concentrations that overlap those in Canada. Hence, the Canadian studies reported PM-related increases in respiratory hospitalizations in children and adults, and cited asthmatics and those with COPD as being susceptible populations. However, the increases in cardiovascular admissions were not statistically significant in some instances, perhaps as a result of limited statistical power. In addition, while the Canadian studies consistently found associations with PM, the respiratory effects were sometimes sensitive to the inclusion of co-pollutants, and there were no co-pollutant analyses in the studies of cardiovascular admissions in Canada.

A limited number of recent studies have examined the shape of the exposure–response relationship between PM and cardiovascular hospital admissions (Zanobetti and Schwartz 2005; Wellenius et al. 2005; Ballester et al. 2006). The results of all of these have indicated that the association is consistent with a linear or near-linear model, with no evidence of a threshold, thereby supporting the findings of earlier assessments. However, there was some indication of regional differences in risk estimates from the largest study of PM_{2.5} effects on hospital admissions for cardiovascular and respiratory diseases. In this study, Dominici et al. (2006) concluded that PM_{2.5} levels were homogenous across the US while the effects were not, suggesting an important role of the geographic variation in PM composition in the observed effects. Respiratory hospital admissions associated with exposure to PM_{2.5} were higher in the west than the east, while the opposite was observed with respect to CVD hospital admissions.

14.5.3 Emergency Room Visits and Other Medical Visits

With the use of administrative data records, ERVs provide a relatively objective and measurable indicator of the impact of PM on public health. Morbidities that result in ERVs are closely related to, but are generally less severe than, those that result in unscheduled hospital admissions. Other medical visits (doctor's office visits, physician visits, general practitioner visits) are less studied but are also very relevant to assessing air pollution public health impacts.

14.5.3.1 Summary of Previous Assessments

In the PM SAD (1999) only six studies, focused solely on respiratory endpoints, were available for review on ERVs and doctor's office visits. Two studies used multi-pollutant regression models to adjust for the confounding effect of co-pollutants. These studies contained limited data on ERVs and PM exposure (one year or two summers, usually in one location), which

provided only limited statistical power for detecting a significant relation. Overall, the results from these studies showed a positive association, although in some cases not statistically significant, between ERVs and various PM metrics (e.g. PM₁₀, PM_{2.5}, and BS). High correlation coefficients between PM and gaseous pollutants were reported, which suggested possible confounding effects of these co-pollutants.

Following the publication of the 1999 PM SAD there was a significant increase in research on the effects of PM on ERV outcomes. Studies were conducted in North and South America, Europe and Asia, covering diverse climates, socioeconomic factors and lifestyles. Using single- and multi-pollutant models, the majority of these studies demonstrated a significant association between PM and respiratory ERVs for children and older adults. The results of most multi-pollutant models showed that gaseous pollutants did not substantially attenuate PM associations.

No formal summary of ERV studies was provided in the US EPA 2004 PM AQCD, as these 23 studies were integrated with results reported for hospital admissions. The associations of all PM indicators with ERVs and other medical visits tended to be less precise than those for hospitalizations, but some studies reported estimates of larger magnitude than those for hospital admissions. It was concluded that these new studies showed positive and generally statistically significant associations between ambient PM levels and increased respiratory-related hospital and medical visits, a conclusion that was generally consistent with, and supportive of, the findings presented by the US EPA (1996). The US EPA 2004 PM AQCD also stated that new studies on primary care settings (daily general practice doctor consultations, private asthma medical visits or visits to primary care health clinics) suggested that limiting studies to only hospital ERVs may greatly underestimate the overall numbers of respiratory morbidity events related to PM. These studies also demonstrated that older adults and the very young are more susceptible to ERVs related to exposure to particulate air pollution. The results from single-pollutant models in the only investigation of cardiac ERVs in older adults showed a significantly positive association with both PM₁₀ and PM_{2.5} but not with SO₄²⁻ or COH. These associations disappeared in multi-pollutant models, suggesting that a large part of the cardiac effects may be attributed to gaseous pollutants.

New time-series studies of ERVs published since 2002 consistently show an association between PM and acute respiratory diseases and support the conclusions reached in the 1999 PM SAD and the US EPA 2004 PM AQCD. In all, 33 studies of ERVs or other related medical visits were reviewed and are summarized below.

14.5.3.2 Respiratory Effects

14.5.3.2.1 All respiratory diseases

In recent years, 19 new studies have investigated the association between daily ERVs for respiratory outcomes and PM air pollution. Most studies were conducted in the US, some in Europe, and the rest either in Asia or Australia. No new studies have been performed in Canada.

Nine studies have investigated the effects of particles on ERVs for all respiratory causes; seven of these have found positive associations, three of them with statistically significant results; only two studies have found negative associations, and these were not statistically significant. Three of the studies were conducted in the US in areas with particle concentrations similar to those found in Canada: two in Spokane, WA (Slaughter et al., 2005; Schreuder et al., 2006) and one in Atlanta, GA (Peel et al., 2005). Both Slaughter et al. (2005) and Peel et al. (2005) examined the association of various particle sizes on ERVs for all respiratory causes (ICD-9 460–519) in all age groups using either Poisson generalized estimating equations (GEEs) or GLMs with

parametric natural cubic splines to adjust for confounding factors. In single-pollutant models, Slaughter et al. (2005) found positive but non-significant associations between ERVs for all respiratory causes and all particle metrics for the study period of January 1995 through June 2001 (with 90% of the daily concentrations of $PM_{2.5}$ ranging from 4.2 to 20.2 $\mu\text{g}/\text{m}^3$ and of PM_{10} ranging from 7.9 to 41.9 $\mu\text{g}/\text{m}^3$). At lag 1 d, a risk increase of 1% (95% CI -2–4%) was observed per 10 $\mu\text{g}/\text{m}^3$ increase in both PM_{10} and $PM_{2.5}$, along with a risk increase of 0.4% (95% CI -0.8–1.6%) per 10 $\mu\text{g}/\text{m}^3$ increase in PM_{10} and $PM_{10-2.5}$. Similar results were also found at lag 2 and 3 d. Significant associations with ERVs for all respiratory causes, as well as for asthma, were only observed for CO. Given the low level of CO during the study period, the authors speculated that CO could represent a marker for combustion particles. Positive and significant associations were, however, found by Peel et al. (2005) in Atlanta, GA, where air pollution data were available for a longer time period (January 1993–August 2000; mean daily ambient PM_{10} and $PM_{2.5}$ of 27.9 and 19.2 $\mu\text{g}/\text{m}^3$, respectively). These researchers found a positive and significant association in single-pollutant models between PM_{10} and ERVs for all respiratory causes with a cumulative lag of 3 d (0–2 d). An excess risk of 1.3% (95% CI 0.4–2.1%) was observed for an increase of 10 $\mu\text{g}/\text{m}^3$ in PM_{10} . Positive but non-significant associations were found for $PM_{2.5}$, $PM_{10-2.5}$ and UFPs, but pollutant data for these particles were only available from August 1998 to August 2000.

Schreuder et al. (2006) also examined the association of $PM_{2.5}$ as well as $PM_{2.5}$ chemical speciation in relation to ERVs for respiratory diseases in Spokane, WA. GAM Poisson regression models and exact GAM SE estimates were used for data analysis, with smoothing splines used to adjust for season and weather factors. Three multivariate receptor algorithms were applied for chemical speciation and eight $PM_{2.5}$ sources were identified, including vegetative burning, As-rich, motor vehicle, sulphate aerosol, nitrate aerosol, airborne soil, Cu-rich and marine. $PM_{2.5}$ data were collected at a residential monitoring site between 1995 and 2002, with a mean daily level of 10.58 $\mu\text{g}/\text{m}^3$. Positive but non-significant associations were found, with an increase of 10 $\mu\text{g}/\text{m}^3$ in $PM_{2.5}$ being linked with excess risks in ERVs for respiratory diseases (1.4% (95% CI -0.4–3.3%) and 1.7% (95% CI -0.1–3.5%) at lag 0 d and lag 1 d, respectively). A higher excess risk was found for ERVs for respiratory diseases in the heating season (1.8% (95% CI -1.5–5.1%)) as compared with the non-heating season (1.6% (95% CI -1.1–4.6%)), with an increase of 10 $\mu\text{g}/\text{m}^3$ in $PM_{2.5}$ at lag 1d. Results from $PM_{2.5}$ source contributors showed that ERVs for respiratory diseases were significantly associated with an increase of 10 $\mu\text{g}/\text{m}^3$ in $PM_{2.5}$ from vegetative burning, with an excess risk of 7.9% (95% CI 3–32.5%) at lag 1 d. Vegetative burning source was a dominant contributor to $PM_{2.5}$ in this area during the winter heating season, and a higher and statistically significant excess risk was also found between all respiratory ERVs and an increment of 10 $\mu\text{g}/\text{m}^3$ in this $PM_{2.5}$ source during the winter season (15.3% (95% CI 2.9–29.3%)). Positive but non-significant results were also observed for As-rich, motor vehicle and airborne soil. These results are discussed in further detail in Section 14.5.7.

Particles have been shown to not be associated with ERVs for respiratory diseases in two studies conducted in Europe; one in Vimercate, Italy (Vegni and Ros, 2004) and the other one in Torrelavega, Spain (Llorca et al., 2005). Vegni and Ros (2004) showed no relation between the number of daily ERVs and daily PM_{10} levels (-0.4% (95% CI -4.6–4.1%)) for an increase of 10 $\mu\text{g}/\text{m}^3$ in same-day PM_{10} (mean daily ambient PM_{10} of 41.5 $\mu\text{g}/\text{m}^3$). Similar results were observed for lag 1 and 2 d. This study was only performed over a 1-year period (September 2001–September 2002) in a small town with only 25,600 inhabitants. Moreover, the daily number of cases was very low (mean = 1.35 \pm 1.27 cases/day). All these facts could have weakened the statistical power to detect an association. Llorca et al. (2005) also observed a non-significant negative association in single-pollutant models between TSP (mean daily level of 48.8 $\mu\text{g}/\text{m}^3$) and ERVs for respiratory diseases in a small Spanish city (-0.2% (95% CI -1.2–

0.8%)) for a 10 $\mu\text{g}/\text{m}^3$ increase in TSP levels. The team noted that given the low number of ERV admissions and the variability in pollutant levels it was difficult to generalize from the results obtained in their study.

Another study led by Linares et al. (2006) in Madrid, Spain, found positive but non-significant associations between PM_{10} (mean daily ambient level of 33.4 $\mu\text{g}/\text{m}^3$) and children's ERVs for respiratory diseases. The team reported that when only the winter season was considered in the analysis the relationship became significant, however (data not shown). Scatter-plot diagrams of the different independent variables and emergency admissions for PM_{10} also showed an apparent threshold of approximately 60 $\mu\text{g}/\text{m}^3$. This team also found a significant increase in children's ERVs for bronchitis with an increment of 10 $\mu\text{g}/\text{m}^3$ in PM_{10} (95% (95% CI 1–16%) at lag 2 d). A PM_{10} mean of 33.4 $\mu\text{g}/\text{m}^3$ was observed in Madrid during the study period.

Some other studies were conducted in areas where climate conditions and PM levels differ from those prevailing in Canada; one study was performed in Asia (Hwang et al., 2004) and the two others in South America (Martins et al., 2002; Farhat et al., 2005). The mean PM_{10} levels in these studies ranged from 48.3 $\mu\text{g}/\text{m}^3$ to 62.6 $\mu\text{g}/\text{m}^3$ while the mean $\text{PM}_{2.5}$ level was 32.1 $\mu\text{g}/\text{m}^3$. All these studies found positive associations between ERVs for respiratory diseases and either $\text{PM}_{2.5}$ or PM_{10} in different age groups.

14.5.3.2.2 Asthma

Asthma is a chronic lung disease in which the airway occasionally constricts and becomes inflamed. Excessive amounts of mucus are also produced in response to an asthma trigger, such as cold or warm air, exercise, emotional stress, viral illness or an environmental stimulant. In many studies around the world, air pollution has been associated with increases in asthma hospitalizations. New studies have also investigated the effects of PM on asthma ERVs. Six out of 10 studies reviewed were performed in the US (Jaffe et al., 2003; Lierl and Hornung, 2003; Michaud et al., 2004; Slaughter et al., 2005; Letz and Quinn, 2005; Peel et al., 2005) while the others were conducted in various areas around the world, including Taiwan (Sun et al., 2006), Australia (Erbas et al., 2005), Spain (Galan et al., 2003) and Turkey (Berktaş and Bircan, 2003). All these studies found positive association between PM and asthma ERVs, either in all age groups or in children; seven found statistically significant results (Berktaş and Bircan, 2003; Galan et al., 2003; Lierl and Hornung, 2003; Michaud et al., 2004; Erbas et al., 2005; Peel et al., 2005; Sun et al., 2006).

In one of the earlier of the US studies reviewed, Jaffe et al. (2003) investigated the relation between summertime asthma ERVs and PM_{10} in Medicaid claimants aged 5–34 years over 5 years in three Ohio cities. Using Poisson regression controlled for time trends and minimum temperature, there was a marginal association (2.3% (95% CI 0–4.8% per 10 $\mu\text{g}/\text{m}^3$ PM_{10}) in Cleveland, the city with the highest mean particulate levels (60.8 $\mu\text{g}/\text{m}^3$). The risk estimates for Cincinnati and Columbus, both of which had average PM_{10} levels of roughly 40 $\mu\text{g}/\text{m}^3$, had wider confidence intervals and varied in direction (one positive, one negative).

Three later all-ages studies in the US examined the association of various particle sizes on ERVs for asthma. For 10 $\mu\text{g}/\text{m}^3$ increases in various PM metrics, positive but non-significant excess risks in ERVs for COPD were found in Atlanta, GA, at lag 0–2 d (Peel et al., 2005) for PM_{10} (0.9% (95% CI -0.4–2.2%)) and $\text{PM}_{2.5}$ (0.5% (95% CI -2.3–3.3%)), while no association was found for $\text{PM}_{10-2.5}$ (-0.2% (95% CI -1.3–3.9%)) or for UFP particle counts (-0.1% (95% CI -2.3–2.1%)). However, when the risk was modelled based on an unconstrained distributed lag (0–13 d), the risk of asthma ERVs was significantly related to PM_{10} (9.9% (95% CI 6.5–13.5%)). The risk estimates for PM_{10} were robust in two-pollutant models with CO, but not with NO₂ or O₃, and reduced almost entirely in four-pollutant models. The mean daily ambient PM_{10} and $\text{PM}_{2.5}$ were 27.9 and 19.2 $\mu\text{g}/\text{m}^3$, respectively. In Spokane, WA (Slaughter et al., 2005), positive but non-

significant associations were also found for each of PM_{10} (3% (95% CI -3–9%)), $PM_{2.5}$ (3% (95% CI -2–9%)), PM_{10} (1% (95% CI -1–3%)) and $PM_{10-2.5}$ (1% (95% CI -1–3%)) for an increase of $10 \mu\text{g}/\text{m}^3$ in PM levels at lag 1 d (with 90% of the daily concentrations of $PM_{2.5}$ ranging from 4.2 to $20.2 \mu\text{g}/\text{m}^3$ and of PM_{10} ranging from 7.9 to $41.9 \mu\text{g}/\text{m}^3$). Another study was conducted by Michaud and collaborators (2004) to assess the impact of volcanic fog exposure on ERVs for respiratory and cardiovascular diseases in Hilo, HI, from January 1997 to May 2001. Volcanic fog (also called “vog”) was measured as SO_2 and PM_{10} ; the hourly PM_{10} average was $1.91 \pm 5.04 \mu\text{g}/\text{m}^3$, while the daily PM_{10} average was $1.91 \pm 2.95 \mu\text{g}/\text{m}^3$. An increase of 13.8% (95% CI 3.0–25%) in asthma/COPD ERVs for all ages was associated with an increment of $10 \mu\text{g}/\text{m}^3$ (lag 1 d) in PM_{10} (mean daily concentration of $1.91 \mu\text{g}/\text{m}^3$).

In the only US study reviewed that specifically investigated children, Lierl and Hornung (2003) found statistically significant associations between pollen count (cumulative lag of 3 d (1–3 d)) and asthma ERVs for children in Cincinnati, OH, with the inclusion of PM_{10} levels (April–October) in the model (monthly means ranging from 28.8 to $42.2 \mu\text{g}/\text{m}^3$). A RR of 1.145 (95% CI 1.076–1.217) was found when PM_{10} levels were less than the median ($33 \mu\text{g}/\text{m}^3$) and of 1.251 (95% CI 1.153–1.358) when PM_{10} levels were greater than the median. The authors concluded that a synergistic effect was observed between pollen counts and particulate matter air pollution.

In Europe, Galan et al. (2003) conducted a time-series study in Madrid, Spain, and observed statistically significant associations between asthma ERVs for all ages in both single- and multi-pollutant models (mean daily PM_{10} concentration of $32.1 \mu\text{g}/\text{m}^3$). In single-pollutant models an excess risk of 3.9% (95% CI 1.0–6.8%) was found for a $10 \mu\text{g}/\text{m}^3$ increase in PM_{10} levels at lag 3 d. Inclusion of pollen into the model did not modify the relationship. Similarly, PM associations remained statistically significant in multi-pollutant models including gaseous pollutants and four types of pollen, with an excess risk of 6.6% (95% CI 2.7–10.7%) with SO_2 and pollen, of 4.4% (95% CI 0.1–9.0%) with NO_2 and of 4.4% (95% CI 1.5–7.3%) with ozone. The mean PM_{10} level in this study was $32.1 \pm 12.1 \mu\text{g}/\text{m}^3$. All these results were obtained with autoregressive Poisson models including parametric modelling of the confounding variables; similar results were also found with Poisson GAM regressions.

In an Australian study, Erbas et al. (2005) found positive and mostly significant associations (at lag 0 d) between an increase of $10 \mu\text{g}/\text{m}^3$ in PM_{10} and increased risks of ERVs for asthma in inner Melbourne (4.7% (95% CI 1.4–8.1%)), eastern Melbourne (2.5% (95% CI 0.3–4.9%)) and south/southeast Melbourne (3.9% (95% CI -1.5–8.6%)). Mean modelled maximum 1-h PM_{10} concentrations ranged from 21.2 to $33.7 \mu\text{g}/\text{m}^3$.

In three studies in which the analyses were somewhat rudimentary, there were significant correlations between ambient PM_{10} and asthma ERVs in children (but not adults) living in Central Taiwan (Sun et al., 2006) and in Ankara, Turkey (Berktas and Bircan, 2003), but no significant correlation with $PM_{2.5}$ for basic military trainees in San Antonio, TX (Letz and Quinn, 2005).

14.5.3.2.3 Chronic obstructive pulmonary diseases

COPD is a group of lung diseases characterized by limitation of airflow in the airways; emphysema and chronic bronchitis are the most common forms. Persons suffering from these chronic respiratory conditions will experience symptoms such as shortness of breath, wheezing, increased mucus and coughing. Four new studies have specifically investigated the impact of particulate air pollution on ERVs for COPD. The two US studies (Peel et al., 2005; Slaughter et al., 2005) examined the association of various particle sizes on ERVs for COPD. For $10 \mu\text{g}/\text{m}^3$ increases in various PM metrics, positive but non-significant excess risks in ERVs for COPD in adults were found in Atlanta, GA, at lag 0–2 d (Peel et al., 2005) for PM_{10} (1.8% (95% CI -0.6–4.3%)) and $PM_{2.5}$ (1.5% (95% CI -3.1–6.3%)) while no association was found for $PM_{10-2.5}$ (-

10.1% (95% CI -19.5–0.6%)) or for UFP counts (-1.8% (95% CI -5.8–2.2%)). However, when the risk was modelled based on an unconstrained distributed lag (0–13 days), the risk of COPD ERVs was significantly related to PM₁₀ (9.2% (95% CI 2.3–16.5%)). The mean daily ambient PM₁₀ and PM_{2.5} concentrations were 27.9 and 19.2 µg/m³, respectively. In Spokane, WA (Slaughter et al., 2005), there were no significant associations found with each of PM₁ (-4% (95% CI -13–5%)), PM_{2.5} (-4% (95% CI -11–4%)), PM₁₀ (0.0% (95% CI -2.9–2.7%)) and PM_{10–2.5} (0.4% (95% CI -2.9–3.5%)) for an increase of 10 µg/m³ in PM levels at lag 1 d (with 90% of the daily concentrations of PM_{2.5} ranging from 4.2 to 20.2 µg/m³ and of PM₁₀ ranging from 7.9 to 41.9 µg/m³).

Two studies were also performed outside the US in areas with high levels of PM. Alves and Ferraz (2005) used a cross-correlation methodology to relate PM₁₀ levels from Oporto, Portugal, with ERVs for COPD and found an inverse relationship between them. The authors concluded that these results could be attributed to missing data resulting from maintenance problems with the sampling instruments and to high levels of precipitation that could have removed particles from the air. Hapcioglu et al. (2006) used multiple stepwise regression analysis to calculate the correlation between meteorological factors, COPD admissions and air pollution in Istanbul, Turkey. A statistically significant correlation was found between ERVs for COPD and PM₁₀ air pollution ($r = 0.28$, $p = 0.03$); when temperature was included in the model the Pearson correlation coefficient was reduced to non-significance ($r = 0.16$, $p = 0.23$).

14.5.3.2.4 Pneumonia

Pneumonia is another lung disease in which the alveoli become inflamed and flooded with fluid; it is a common illness and occurs in all age groups. Positive but non-significant links were observed in Hawaii (Michaud et al., 2004) between ERV admissions in all age groups due to influenza, colds and pneumonia and a 10 µg/m³ increase in PM₁ (mean daily concentration of 1.91 µg/m³) at lag 1 d (4% (95% CI -14–26%)) and lag 3 d (11% (95% CI -5–29%)). Peel et al. (2005) also found positive but non-significant pneumonia risk increases in Atlanta, GA, and an increase of 10 µg/m³ at lag 0–2 d in PM_{2.5} (1.1% (95% CI -1.9–4.2%)) and PM₁₀ (1.1% (95% CI -0.4–2.7%)) (mean daily ambient PM_{2.5} and PM₁₀ were 9.2 and 27.9 µg/m³, respectively). However, when the risk was modelled based on an unconstrained distributed lag (0–13 d), PM₁₀ was significantly related to the increased risk of ERVs for pneumonia (8.7% (95% CI 4.4–13.2%)), as well as for URTI (7.3% (95% CI 4.8–9.9%)).

14.5.3.3 Cardiovascular Effects

Among the recently published literature eight new studies have investigated the health effects of PM on daily ERVs for cardiovascular outcomes.

One study performed by Villeneuve and collaborators (Villeneuve et al., 2006a) was conducted in Edmonton, AB, between April 1, 1992 and March 31, 2002. The team undertook a time-stratified case-crossover study to evaluate the association between outdoor air pollution and ERVs for ischemic stroke, hemorrhagic stroke and transient ischemic stroke attacks (TIAs) in adults ≥65 years of age. Mean 24-h PM levels measured throughout the study period were 8.5 µg/m³ ± 6.2 and 24.2 µg/m³ ± 14.8 for PM_{2.5} and PM₁₀, respectively. PM levels during the summer periods were a bit higher. In the summer season, positive but non-significant increases in ischemic stroke were found with increments of 10 µg/m³ in PM_{2.5} (7.8% (95% CI -3.1–20.7%)) and PM₁₀ (2.8% (95% CI -2.9–8.3%)) in single-pollutant models for a 3-d mean. Positive but non-significant associations with hemorrhagic stroke were also observed in single-pollutant models for a 3-d mean: for PM_{2.5}, 17.4% (95% CI -9.1–51.5%) and for PM₁₀, 6.1% (95% CI -5.8–19.7%). For ischemic stroke, positive and significant results were obtained with both NO₂ and CO in the summer, while no significant associations were observed in winter analyses with any pollutants. Similar results were found for hemorrhagic stroke, but with SO₂ and CO, while only

SO₂ in the summer season was significantly associated with TIAs. In two-pollutant models risk estimates for both CO and NO₂ increased in the presence of PM, while the NO₂ risk estimates were modestly attenuated with the addition of CO to the model. The team concluded that vehicular traffic, which contributes to increased levels of NO₂ and CO, may have contributed to the increased incidence in ERVs for stroke. The authors also stated that they had limited statistical power to characterize the PM-related risks.

Other teams have also looked at the relationship between PM and ERVs for stroke in several locations: Sao Paulo, Brazil (Lin et al., 2003); Sydney, Australia (Jalaludin et al., 2006); and Taipei, Taiwan (Chan et al., 2006). GLMs were used by Jalaludin et al. (2006) to determine the associations between daily air pollution in Sydney and ERVs in adults ≥65 years of age for all CVDs, cardiac diseases, IHD and stroke). PM levels in this study were comparable with levels usually found in Canada; mean daily PM_{2.5} and PM₁₀ levels were 9.5 µg/m³ and 16.8 µg/m³, respectively. This team also included BS particles in their analyses. Results for BS were expressed as percentage change (and 95% CI) in CVD ERV attendances per 0.18/10⁴/m increase for BS particles. Positive and significant associations were observed in single-pollutant models between BS and all CVDs (1.05% (95% CI 0.44–1.66%) at lag 0 d) and cardiac diseases (1.34% (95% CI 0.63–2.05%) at lag 0 d, 0.83% (95% CI 0.10–1.57%) at lag 1 d and 1.13% (95% CI 0.44–1.82%) at lag 0–1 d). A significant increased risk was also observed between increments of 10 µg/m³ in PM₁₀ and cardiac diseases (1.47% (95% CI 0.18–2.79%) at lag 0 d). Significant associations were also found between PM_{2.5} and all CVDs (2.63% (95% CI 1.17–4.08%) at lag 0 d); cardiac diseases (3.23% (95% CI 1.54–4.96%) at lag 0 d, 1.90% (95% CI 0.17–3.65%) at lag 1 d, and 2.77% (95% CI 1.13–4.45) at lag 0–1 d); and IHD (2.58% (95% CI 0.08–5.10) at lag 0–1 d). NO₂ and CO were also significantly associated with all CVDs, cardiac diseases and IHD, while SO₂ was significantly associated with all CVDs and IHD. The effects of air pollutants were generally greater in the cool period as compared with the warm period. In two-pollutant models the effects of CO, O₃, NO₂ and SO₂ were essentially unchanged, while particulate effects were greater when O₃ was added to the model but decreased when NO₂ or CO was added (results only presented in figures). This study adds to the growing evidence that air pollution affects cardiovascular outcomes. The levels of PM reported in the studies performed in Brazil (Lin et al., 2003) and Taiwan (Chan et al., 2006) were much higher than those encountered in Canada (mean PM levels >30 µg/m³). Even at these high levels only positive non-significant associations were observed between PM and ERVs for stroke in adults aged 45–80 (Lin et al., 2003) or >50 (Chan et al., 2006), similar to the results noted by Villeneuve et al. (2006a). However, in the Taiwanese study (Chan et al., 2006) both PM_{2.5} and PM₁₀ were significantly associated with ERVs for cerebrovascular diseases in single-pollutant models, though in multi-pollutant models with gaseous air pollutants, these associations, while still positive, did not remain significant.

In Atlanta, Metzger and collaborators (Metzger et al., 2004) investigated the effects of ambient air pollution on ERVs for specific causes of CVD, including dysrhythmia, CHF, IHD and peripheral vascular disease. The team used air pollution and ERV data from either January 1, 1993, to August 31, 2000, or from August 1, 1998, to August 31, 2000. This latest period was called the ARIES (Aerosol Research and Inhalation Epidemiology Study) period, where an air quality monitoring station was installed near downtown to estimate levels of PM_{2.5} and its physicochemical components. Gaseous pollutants were also measured continuously during this period. Median values for PM_{2.5}, PM₁₀ and PM_{10–2.5} were 17.8 µg/m³, 26.3 µg/m³, and 9.1 µg/m³, respectively. The investigators also looked at EC, OC, PM_{2.5}, sulphates and acidity. Data were analyzed with Poisson GLMs, controlling for long-term temporal trends and meteorological conditions (temperature and dew point) with natural cubic splines to avoid GAM issues. Indicator variables were also included into the model for the day of the week, hospital entry and exit as well as holidays. Sensitivity analyses were performed by varying the frequency of knots

for cubic splines in GLM analyses and assessing day-to-day serial correlation in GEEs. Associations were also investigated with GAM non-parametric LOESS smoothers and non-parametric smoothing splines to compare results from different models, and seasonal analyses for warm and cool periods were conducted. Age-specific analyses were also explored (adults ≥ 19 and >65 years). In single-pollutant models, the excess risk of ERVs for all CVDs from an increase of $10 \mu\text{g}/\text{m}^3$ (3-d moving average) was 3.3% (95% CI 1.0–5.6%) for $\text{PM}_{2.5}$, 13.7% (95% CI 3.0–13.2%) for OC and 21.9% (95% CI 5.1–42.4%) for EC. Excess risks of ERVs for CHF were also statistically associated with $\text{PM}_{2.5}$ (5.5% (95% CI 0.6–10.5%)), OC (26.4% (95% CI 3.5–54.6%)) and EC (41.1% (95% CI 3.0–93.1%)). An increased risk of 5.0% (95% CI 0.8–9.3%) was also found for ERVs for peripheral vascular disease, with an increment of $10 \mu\text{g}/\text{m}^3$ in $\text{PM}_{2.5}$. In age-specific analyses, associations between CVD visits and air pollution were similar among the adult group and the older adult group. Positive but non-significant relationships were found between a $10 \mu\text{g}/\text{m}^3$ increase in coarse PM and all CVDs (2.4% (95% CI -3.0–8.2%)), dysrhythmia (4.2% (95% CI -5.1–14.5%)) and peripheral vascular disease (4.3% (95% CI -5.5–15.3%)), while no association was found with IHD (-1.2% (95% CI -10.5–9.2%)). NO_2 and CO were also significantly associated with ERVs for all CVDs, IHD and peripheral vascular disease. All associations were robust to model structure and specification; similar point estimates were observed with GLMs using alternative frequencies of knots as well as with models using GAMs. Multi-pollutant models were also carried out but only for ERVs for all CVD visits that were statistically significant in single-pollutant models. OC and EC were combined together as total carbon, given the fact that they were highly correlated ($r = 0.82$). The numbers of days included in multi-pollutant models were all reduced, since only days with non-missing data were included. For the entire period (1993–2000), estimates for NO_2 were slightly reduced in two-pollutant models, while the estimate for CO was indistinguishable from the null. By contrast, for the ARIES period (1998–2000) the estimates for CO were similar in two-pollutant models with $\text{PM}_{2.5}$, NO_2 and oxygenated hydrocarbons. The estimates for $\text{PM}_{2.5}$, NO_2 , total carbon and oxygenated hydrocarbons were generally attenuated and indistinguishable from the null in two-pollutant models. Similar patterns were also observed in three-, four-, and five-pollutant models.

ERVs for CVDs from January 1992 to December 1995 were not significantly associated with TSP levels (mean daily $48.8 \mu\text{g}/\text{m}^3$) for people living in Torrelavega, Spain (60,000 inhabitants) (Llorca et al., 2005). Given the small number of ERVs and the variability in pollutant levels it is impossible to draw specific conclusions based on this research. The authors also suggested rain as a factor that could have reduced the observed PM-related health effects.

Increased risks in ERVs for CVD (IHD, dysrhythmias and HF) were also observed by Hwang et al. (2004) in an area with high levels of PM (Taipei, Taiwan) where significant associations ($p < 0.05$) were found for both $\text{PM}_{2.5}$ and PM_{10} in the all-ages category. Another study was conducted by Michaud and collaborators (2004) to assess the impact of volcanic fog exposure on ERVs for respiratory and cardiovascular diseases in Hilo, HI, from January 1997 to May 2001. Volcanic fog was measured as SO_2 and PM_1 ; the hourly PM_1 average was $1.91 \pm 5.04 \mu\text{g}/\text{m}^3$, while the daily PM_1 average was $1.91 \pm 2.95 \mu\text{g}/\text{m}^3$. A positive but non-significant increased risk of 7% (95% CI -13–30%) at lag 1 d was found between a $10 \mu\text{g}/\text{m}^3$ increase in PM_1 and ERVs for cardiac diseases among people living in this area.

14.5.3.4 Other Medical Visits

Nine new studies looked at other medical visits, including five covering visits to clinics or physicians (Hwang and Chan, 2002; Bakonyi et al., 2004; Chang et al., 2006; Villeneuve et al., 2006b; Wong et al., 2006). One study investigated the relationship between air pollution and doctor's house calls (Chardon et al., 2007) and another study, based on physician-visit billing data, investigated the population health effects of changes in air quality due to forest fires in

British Columbia (Moore et al., 2006). A unique study was also performed to investigate the association of air pollution and respiratory visits in an ambulatory care setting (Sinclair and Tolsma, 2004). Most of these studies looked at respiratory health outcomes (allergic rhinitis, asthma, URD or URTIs, lower respiratory disease or tract infections (LRD or LRTIs) or all respiratory diseases); only one included CVD in the study design (Moore et al., 2006). One study also examined the association of air pollution in Paris, France, with a new health outcome, ophthalmological emergency examinations (Bourcier et al., 2003). These studies were conducted throughout the world (Toronto, Kelowna and Kamloops, Canada; the US, Europe, Asia and South America) and investigated the relationship of various PM metrics (PM₁₀, PM_{2.5}, PM_{10-2.5}, smoke, UFPs) with health outcomes.

Allergic rhinitis, often called hay fever, occurs when the body's immune system reacts to allergens in the air, causing symptoms such as sneezing and a runny nose. Few studies have examined the association between allergic rhinitis and ambient air pollution. In two earlier studies, gaseous pollutants were important predictors of general practitioner consultations for allergic rhinitis and effects were more pronounced in children than adults in London, UK (Hajat et al., 2001), and no association was observed between air pollution and prevalence of rhinitis in children in France (Ramadour et al., 2000). One Canadian study (Villeneuve et al., 2006b) recently investigated the relationship between PM (PM₁₀, PM_{2.5}, PM_{10-2.5}), ragweed particles, and gaseous pollutants (CO, NO₂, SO₂, O₃) and allergic rhinitis among adults ≥65 years old between 1995 and 2000. The study, performed in metropolitan Toronto, ON, suggested that outdoor air pollution is a poor predictor of physician visits for allergic rhinitis among the older adult population. This study used a population-based administrative database tabulated from the Ontario Hospital Insurance Plan. The relationship was studied with GLMs while controlling for long-term trends and meteorological factors (temperature and relative humidity) with natural cubic splines. Indicator variables were also included in the model to control for day of the week as well as for holiday effects. The association between outdoor air pollution and rhinitis was also adjusted for aeroallergens (pollen grains and fungal spores). Various lag structures were studied (single-day to lag 0–6 d) and analyses were performed for the full year as well as individually for summer (May–October) and winter (November–April) seasons. Only single-pollutant models were tested. The percentage changes in the number of physician visits were presented per IQR increase in air pollutant. No significant associations were found between TEOM-based measures of PM₁₀, PM_{2.5} and gaseous pollutants or dichot-based measures of PM₁₀, PM_{2.5} and coarse PM with allergic rhinitis in all-year, summer and winter season analyses. Positive but non-significant effects were, however, found with all particulate measures with various lag structures, although no specific patterns could be highlighted. Higher estimates were observed for coarse PM in the summer season as compared with PM_{2.5} or PM₁₀ while significant effects were only found between rhinitis and particle levels of ragweed, a compound known to induce rhinitis in some individuals. The team concluded that the analysis suggested air pollution exerts at most a minor effect on the exacerbation of rhinitis in the older adult population.

The health effects of PM associated with burning vegetation have not been extensively studied. In fact, Moore's team (Moore et al., 2006) was the first to investigate the health effects of such events in a Canadian population. The interior of British Columbia, including Kelowna and Kamloops, experienced 5 weeks of elevated PM levels in the summer of 2003 due to forest fires (daily peak PM_{2.5} was 140 µg/m³ in Kamloops and 200 µg/m³ in Kelowna). Moore and collaborators investigated whether PM_{2.5} and PM₁₀ were associated with any changes in physician visits for respiratory, cardiovascular and mental illnesses during 2003 as compared with aggregate rates of the previous 10 years. They used population-based long-term physician billing data to estimate the relationship between physician visits and increased air pollution levels. It was found that increases in Kelowna residents' physician visits for respiratory complaints were associated with forest fire smoke, while no association was found for physician

visits due to CVD or to mental illness. Increases in physician visit rates for respiratory complaints were respectively 46%, 54% and 78% for three different weeks during the summer 2003 fire period. In Kamloops, no significant associations were found with visits for any respiratory or cardiovascular conditions, or mental illness, probably due to the lower levels of PM observed in this area and the smaller number of people living there, which increased the variability in the data.

Hospital admission and ERV data published since 2002 consistently showed an association between PM and acute respiratory diseases. Two new studies looked at respiratory visits for asthma, URDs, URTIs, LRDs and LRTIs in either ambulatory care settings (Sinclair and Tolsma, 2004) or based on doctors' house calls (Chardon et al., 2007). The study by Sinclair and Tolsma (2004) used data collected as part of the in-depth 25-month ARIES program (August 1998–August 2000) in Atlanta, GA (mean daily PM₁₀ and PM_{2.5} levels were 29.03 and 17.62 µg/m³, respectively). Positive and significant associations ($p < 0.05$) were found between adult asthma and UFP area (RR = 1.223; confidence intervals not presented) for the 3–5 d lag based on one standard deviation, which corresponded to 244.09 nm. For child asthma, positive and significant increased risks ($p < 0.05$) were found with coarse particles (11.5%), PM₁₀ (4.2%), EC (38.5%) and OC (22.7%) at lag 3–5 d for an increase of 10 µg/m³. For URTIs, significant associations were found with UFP area (RR = 1.041; standard deviation of 244.09 nm) at lag 0–2 d and with coarse particles at lag 3–5 d (excess risk = 4.5%; increment of 10 µg/m³). LRTIs were found to be significantly associated with PM_{2.5} acidity and SO₂ at lag 0–2 d as well as with coarse particles, PM₁₀, EC, OCPM_{2.5} water-soluble metals at lag 3–5 d and UFP area at lag 6–8 d. Given the multiple limitations in this study (the healthcare settings are not representative of many outpatient healthcare models, 12% of all visits were not coded for appointment type, only single-pollutant models were used, etc.) these results should be interpreted with caution. However, the team concluded that since positive and significant associations were found in this study, primary care setting data can be a useful additional resource for air quality epidemiological research. Similar results were found by Chardon et al. (2007) in Paris, France (mean daily PM₁₀ and PM_{2.5} levels were 23 and 14.7 µg/m³, respectively). Positive and significant associations were observed between doctors' house calls for URDs and LRDs and an increase of 10 µg/m³ in PM₁₀ (2.9% (95% CI 0.8–5.1%) and 3.1% (95% CI 0.9–5.4%), respectively) and PM_{2.5} (6.0% (95% CI 3.1–9.1%) and 5.8% (95% CI 2.8–8.95%), respectively). Positive but non-significant associations were found with doctors' house calls for asthma. Results obtained in this study confirm the higher sensitivity of doctors' house calls for respiratory illness as a health indicator.

Some other studies (Bourcier et al., 2003; Hwang and Chan, 2002; Bakonyi et al., 2004; Chang et al., 2006; Wong et al., 2006) were conducted in areas with much higher levels of air pollution than Canada. Beside eye irritation, there is very little information on the effects of air pollution on the ocular system. High levels of air pollution were shown to be associated with visits to the ophthalmological emergency centre for conjunctivitis in Paris, France, in 1999 (Bourcier et al., 2003) when the mean daily concentration of PM₁₀ was 218.3 µg/m³. However, only NO and NO₂ were statistically associated with emergency visits for conjunctivitis; the excess risk associated with an increase of 10 µg/m³ in PM₁₀ was positive but non-significant (0.6% (95% CI -0.1–1.4%)). Two studies (Hwang and Chan, 2002; Chang et al., 2006) were performed in Taiwan with mean levels of PM₁₀ ranging from 59.9 to 110.37 µg/m³. Hwang and Chan (2002) used data obtained from clinic records and environmental stations in Taiwan during 1998 to estimate the association between air pollution and daily numbers of clinic visits for LRTIs; they found positive and significant associations in children and older adults in both single- and multi-pollutant models. People >65 years of age were the most susceptible, and estimated pollution effects decreased as the exposure time lag increased. Chang et al. (2006) observed positive but non-significant associations between Asian dust storm events and clinic visits for allergic rhinitis,

with an increased risk of 3.6% (95% CI -0.4–64.9%) for an increment of 10 $\mu\text{g}/\text{m}^3$ in PM_{10} at lag 2 d. This finding could be attributed to the low number of clinic visits for allergic rhinitis during the study period, which may have resulted in a lack of statistical power to detect a significant association. Both BS and PM_{10} were marginally significantly associated with respiratory disease health centre attendance among children <14 years of age in Brazil at lag 0 d, and 2- and 3-d moving averages (Bakonyi et al., 2004). Another study (Wong et al., 2006) impacted by GAM issues found positive and significant associations between general practitioner visits for URTIs in Hong Kong and an increase of 10 $\mu\text{g}/\text{m}^3$ in PM_{10} (2.0% (95% CI 1.6–2.5%)). Similar results were also observed with $\text{PM}_{2.5}$ (2.1% (95% CI 1.0–3.2%)).

14.5.3.5 Summary and Considerations: Emergency Room Visits and Other Medical Visits

Recent ERV data usually supported findings from respiratory hospitalization studies, as increases in ambient PM levels were associated with significantly increased visits to emergency rooms. In this section 33 peer-reviewed ERV and other medical-related visit studies published since October 2002 have been reviewed. These studies were conducted in North and South America, Europe and Asia, and included diverse climates, socioeconomic factors and lifestyles. Studies of the acute effects of PM using ERVs or other related medical visits (clinic visits, ambulatory care settings, general practitioner visits, doctors' house calls) have considered various outcomes, ranging from all-respiratory causes or specific respiratory diseases (asthma, URTI, LRTI, allergic rhinitis) to conjunctivitis or CVD. Since ERVs for diseases such as asthma attacks and respiratory illness are more frequent than hospitalizations, they usually generate larger databases. It is therefore easier to investigate specific diseases (e.g. asthma, COPD) rather than broad disease categories such as "respiratory diseases." These new studies validate earlier research showing a strong relationship between PM and visits to the emergency room or to medical clinics due to respiratory health effects.

The scientific database on respiratory ERVs and medical visits has grown since 2002 and new studies consistently report associations between PM and acute respiratory diseases; seven out of nine studies found positive associations. The strongest PM-related associations were observed with asthma ERVs; all studies looking at this relationship reported positive associations, and 7 out of 10 studies showed statistically significant associations. In one study, asthma and COPD ERVs were associated with PM_1 in an all-age group, but the association between PM and ERVs for COPD was inconsistent across studies. The PM-related associations remained significant after modelling for pollen and gaseous pollutants. In two studies, all-year-round positive non-significant estimates became significant in winter-only analyses. Other positive but non-significant estimates were linked to a lack of PM data, short study periods, or few cases, which have limited statistical power.

Studies of pollution-related effects and primary care settings were first described in the US EPA 2004 PM AQCD. Since that time there have been more studies, which generally suggest that other means of measuring access to the health care system may provide additional evidence of the health effects associated with exposure to air pollution. PM was associated with respiratory endpoints diagnosed during doctors' house calls, visits to family practitioners and in primary ambulatory care settings. A Canadian study (Villeneuve et al., 2006b) suggested that outdoor air pollution is a poor predictor of physician visits for allergic rhinitis in older adults, similarly to an earlier study in children (Ramadour et al., 2000).

Children differ physiologically from adults: their lungs are under development and their body's defences are also still developing, so they have more respiratory infections. As they are outside for longer periods and are usually more active than adults, they may be more susceptible to the effects of PM. Results from Sinclair and Tolsma (2004) demonstrated that children's respiratory

systems seemed more impacted by airborne PM than those of adults. For adults, positive and significant results were only found between asthma and UFPs, while for children significant associations were observed for asthma, URIs and LRTIs with various PM metrics (EC, OC, PM₁₀, PM_{10-2.5}, PM_{2.5}, UFPs). Sun et al. (2006) also found a statistically significant correlation between PM₁₀ and asthma ERVs for children living in central Taiwan as well as a non-significant correlation in adults. Another study (Linares et al., 2006), performed in Madrid, Spain, did find a positive, while non-significant, association between PM₁₀ and children's ERVs for respiratory diseases. The team reported, however, that when only the winter season was considered the relationship became significant (data not shown). Lierl and Hornung (2003) also found statistically significant associations between childhood asthma ERVs and PM₁₀.

Only one study published before 2002 investigated the relationship between PM and ERVs for cardiovascular outcomes. Since then, eight new studies have analyzed the health effects of PM on daily cardiovascular ERVs for all CVDs, ischemic or hemorrhagic stroke, CHF, dysrhythmia and cerebrovascular diseases. All these studies have found positive associations between various PM metrics and cardiovascular ERVs, and five of them showed statistically significant associations. One well-designed study observed similar findings in subjects >19 years of age and subjects >65 years of age; however, the effects of PM metrics disappeared in two-pollutant models with gaseous pollutants. Results across other studies are not entirely consistent with these findings: with respect to the susceptible age groups that have been identified; some studies indicate that adults and older adults share similar risks, and others suggest that older adults may be more at risk. In addition, while PM-related CVD outcomes were sometimes attenuated by adjustment for co-pollutants, in some models they remained significant. The rate of physician visits for CVD in British Columbia was not associated with forest fire smoke, a similar finding to previous North American studies in which vegetation burning was not related to physician visits for CVD. However, this may indicate that physician visit data are not adequately sensitive to detect effects such as circulatory diseases that may be associated with elevated PM levels.

It is worth noting that almost all new studies used only single-pollutant models to study the relationship between particulate air pollution and ERVs or other types of medical visits. Because of the various PM metrics (PM₁, PM_{2.5}, PM_{10-2.5}, PM₁₀, BS particles and TSP) used in the ERV studies no overall risk estimate has been drawn from these studies. New time-series studies of hospital admissions and ERVs published since 2002 have, however, consistently shown an association between PM and medical visits for acute respiratory diseases, especially with asthma and mostly in children but sometimes in adults. These studies support conclusions reached in the 1999 PM SAD and the US EPA 2004 PM AQCD. The results of new studies have also suggested that PM may be linked with ERVs for CVDs.

14.5.4 Other Health Outcomes

14.5.4.1 Summary of Previous Assessments

In addition to traditional health outcomes that have been associated with PM, such as mortality, hospital admissions and ERVs or medical visits, other health indicators have been associated with air pollution (e.g. school absenteeism, asthma medication and respiratory drug use) in time-series studies. In the 1999 PM SAD one study investigated the association between PM₁₀ levels and school absenteeism in the Utah Valley between 1985 and 1990 using a time-series approach (Ransom and Pope, 1992). The average absenteeism rate was found to be higher during periods of relatively high PM₁₀ than during periods of low PM₁₀. However, this study did not take into account all of the potential confounding factors that could influence school

absenteeism. The effects of ambient air pollution on school absenteeism due to respiratory illnesses were also studied by Gilliland et al. (2001) in a sub-cohort of the Southern California Children's Health Study (CHS) and reviewed by the US EPA (2004). Only a short-term change in ozone was associated with a substantial increase in school absences from both lower and upper respiratory illness; no associations were observed with NO₂ and PM₁₀. No conclusions on these health outcomes were reached either in the 1999 PM SAD or the US EPA 2004 PM AQCD due to the limited number of publications on this topic.

A few studies published since 2002 have investigated the effects of PM on school absenteeism, asthma medication in children and the impact on drug sales.

14.5.4.2 Medication Use and Drug Sales

Respiratory drug use is frequent following medical consultation and, in many countries, a prescription is a mandatory requirement to gain access to these medications. Medication use has also been assessed in panel studies (see Subsection 14.5.2.2).

In Anchorage, AK, Gordian and Choudhury (2003) investigated the relationship between the use of asthma medication in schoolchildren and PM from September 1994 to December 1997. The 24-h PM₁₀ concentration averaged 36.11 µg/m³ ± 30.46, and ranged from 2.96 to 210.0 µg/m³. Nurses' records of asthma medication use in elementary schoolchildren were selected as the indicator. PM₁₀ moving averages lagged at 7, 14, 21 and 28 d were used in regression models controlling for temperature, time trend and day of the week as potential confounders. A dummy variable was used to account for month as a potential confounder. All models yielded positive associations between PM₁₀ and medication use. The strongest association (coefficient 7.25, SE 2.88, p = 0.01) was observed between PM₁₀ and asthma medication for a 21-d moving average. In this study an association was also observed between PM₁₀ and asthma in an area where the major constituent of PM₁₀ was coarse particles (85%), primarily silico-aluminum-based.

Two studies evaluating the impact of air pollution on drug sales were also performed in Europe. In Rouen, France, Pitard et al. (2004) conducted a time-series study to look at the impact of BS on drug sales (anti-asthmatic, bronchodilator and cough/cold) between July 1998 and June 2000, while Vegni et al. (2005) carried out a similar study in Como, Italy, by looking at the impact of TSP on respiratory drug dispensing data. In the French study (Pitard et al., 2004) the mean daily BS was 16.7 µg/m³ with a range of from 2 to 126 µg/m³; other pollutants (NO₂, SO₂) were also assessed. Poisson GAMs were used with non-parametric LOESS smoothers to control for trends and meteorological factors (temperature and humidity). Dummy variables to control for the day of the week as well as holidays were also included in the model. The effect of influenza epidemics was also taken into account as an explanatory variable. A polynomial distributed lag model with lags of up to 10 d was used and results for BS were based on an increment of 10 µg/m³. For anti-asthmatic and COPD products, statistically significant associations (p < 0.05) with a 10 µg/m³ increase in BS were found with 1–7 d lags; the highest excess risk was for a 3-d lag (0.8% (95% CI 0.3–1.4%)). Statistically significant associations were also observed with NO₂ while no association was found with SO₂. For cough and cold preparation products, associations were also observed for lags ranging from 1 to 9 d, the highest excess risk being for a 5-d lag (1.1% (95% CI 0.8–1.3%)). Statistically significant associations (p < 0.05) were also found for 9-d lag SO₂ and for lags ranging from 3 to 9 d with NO₂. In an age group analysis, statistically significant associations (p < 0.05) were found for children 0–14 years of age using anti-asthma and COPD products. The highest significant increased risk for BS was with the 9-d lag (0.9% (95% CI 0.2–1.7%)). Statistically significant associations were also observed with NO₂ while no association was found with SO₂. For cough and cold preparation products, associations were found for lags ranging from 2 to 9 d with SO₂, NO₂ and BS. The highest significant excess risks for BS were with 6- and 7-d lags (1.3% (95%

CI 0.8–1.8%) and 1.3% (95% CI 0.7–1.8%), respectively). For people aged 15–64, statistically significant associations ($p < 0.05$) were found with anti-asthmatic and COPD products for the 5- and 6-d lags with NO_2 only. Cough and cold preparation products also revealed statistically significant associations for 1-, 8- and 9-d lags with SO_2 , for 5–9 d lags with NO_2 , and for 6- and 8-d lags with BS. No associations were found for NO_2 , SO_2 , or BS with both anti-asthmatic and COPD products as well as with cough and cold preparations for people 65–74 years old. For people >75 , statistically significant associations were only found with SO_2 and NO_2 .

The other study conducted in Italy (Vegni et al., 2005) looked at the relationship between respiratory drug use and air pollution. An analysis of log transformed data was conducted with a Poisson regression model, using a weekly time period and controlling for long-term trends, seasonal variations and holidays. Weather variables were accounted for using likelihood ratio tests. Further analysis was done with a random effects Poisson model to account for serial correlation by adjusting SEs for temporal clustering. Two variables were defined as the health indicators: the total number of individuals having at least one respiratory drug dispensed during the week (cases) and the total weekly sum of daily defined doses of respiratory drugs dispensed (DDD). For an increase of $10 \mu\text{g}/\text{m}^3$ in TSP, the excess risks for count of individuals with at least one dispensed drug and DDD were respectively 1.3% (95% CI 0.0–2.5%), $p < 0.044$, and 2.1% (95% CI 0.7–3.4%), $p < 0.002$. Additional analysis also indicated significant effects for both endpoints in the upper three quintiles of TSP ($>53.9 \mu\text{g}/\text{m}^3$, 53.9 to $<65.5 \mu\text{g}/\text{m}^3$ and 79.2 to $<187.6 \mu\text{g}/\text{m}^3$).

Overall, these studies have shown that drug sales can serve as a useful health indicator for providing information on daily variations under conditions not requiring medical care. With drug sales as an health indicator it is possible to conduct an epidemiological time-series in a very small geographical area, and significant associations have been found with various air pollution indicators, including TSP, PM_{10} and BS.

14.5.4.3 School Absenteeism

Two studies investigated the impact of PM on school absenteeism in South Korea (Park et al., 2002) and in California (Rondeau et al., 2005).

Park et al. (2002) used a time-series design to assess the association between air pollution and school absenteeism among elementary students for the period from March to December 1999 in Seoul, Korea. Levels of PM_{10} were measured by a β -absorption method and the mean (range) for the study period was $68.11 \mu\text{g}/\text{m}^3$ (10.47–190.16). Gaseous pollutants were also measured and included in the analysis (CO, SO_2 , NO_2 and O_3). Relationships were analyzed with GAM with LOESS to account for time and weather confounders and several lag structures were considered (same-day, 1-d lag and 7-d moving average). Single- and two-pollutant models were used to estimate effects. The excess risks for an increase of $10 \mu\text{g}/\text{m}^3$ in PM_{10} for total absences, non-illness-related absences and illness-related absences were, respectively, 0.2% (95% CI -0.2–0.7%), -0.5% (95% CI -1.2–0.5%) and 1.4% (95% CI 0.9–2.1%). Significant associations for illness-related absences were also found with ozone and SO_2 . In bivariate analyses, the effect of PM_{10} was no longer significant with SO_2 (0.7% (95% CI -0.2–1.4%)) but remained significant with ozone (1.4% (95% CI 0.9–1.8%)). Relationships between gaseous pollutants and school absenteeism remained stable and significant in all analyses. PM_{10} and SO_2 were moderately correlated ($r = 0.60$) and a very low correlation was observed between PM_{10} and ozone ($r = 0.07$).

Rondeau et al. (2005) proposed a three-level model to examine the effects of daily exposure to air pollution and individual risk factors on health outcomes; they then applied this model to a study of the effects of air pollution on school absenteeism in a sub-cohort of the CHS in California. The Air Pollution and Absence Study (Gilliland et al., 2001) monitored the number

and types of absences during the first 6 months of 1996 for a sub-cohort of 1932 children 9–10 years old in 12 communities. The new model simultaneously treated daily exposure to air pollution and individual risk factors without aggregating over subjects or time. Effects of individual or household characteristics on the incident absences probabilities were evaluated. Age at entry was not significantly associated with absence outcomes and no significant interaction was found between age and sex. A significant association was, however, found between any type of absenteeism and body mass index (BMI), household income (\leq \$14,999) and the day of the week (Monday, Wednesday and Thursday). For respiratory-illness-related absences, children who had ever been diagnosed as asthmatic had an increased risk of being absent, while an increment of $10 \mu\text{g}/\text{m}^3$ for a 30-d lagged PM_{10} exposure was significantly associated with all absences (8.6% (95% CI 3.2–14.3%)) but not with illness-related absences.

14.5.4.4 Summary and Considerations: Other Health Outcomes

The new studies have shown that drug sales or medication use can serve as useful health indicators to provide information on daily variations under conditions not requiring medical care nor involving serious cases such as death or admission to hospital. With drug sales as a health indicator it is possible to conduct epidemiological time-series studies in a very small geographical area, and significant associations have been found with various air pollution indicators, including TSP, PM_{10} and BS. However, the limited nature of the most recent studies precludes us from drawing any strong conclusions. One study (Pitard et al., 2004) was limited by the use of GAMs and the other two studies (Gordian and Choudhury, 2003; Vegni et al., 2005) provided information primarily on larger fractions (TSP and $\text{PM}_{10-2.5}$).

The results of studies reviewed in earlier assessments have suggested that air pollution is associated with school absenteeism; however, associations with PM_{10} were weakened in one study (Ransom and Pope, 1992) by lack of consideration of potential confounders and were not significant in a second study (Gilliland et al., 2001). The limited recent literature has provided little additional information. In one study limited by the use of GAMs, PM_{10} was associated with illness-related absences in a single-pollutant model and in a two-pollutant model with ozone but not with SO_2 (Park et al., 2002). In a second study (Rondeau et al., 2005) PM_{10} was associated with all absences but not with illness-related absences. Since the relationship between PM and school absenteeism has only been examined in four studies, the data are currently too limited to draw any strong conclusions.

14.5.5 Panel Studies

Panel studies are epidemiological studies designed to examine groups of people engaged in normal activities in the natural environment in which pollutant levels may be closely monitored, and exposures are usually to the ambient mix of pollutants. These studies have the advantage that subjects of all ages and health status may be included. In addition, it is possible to track subjects' medical histories, episodes of illness, lifestyles and activity patterns. Endpoints are repeatedly measured, and may include clinical, biochemical or physiological changes. Even with a small number of subjects, repeated measurements can maximize information and increase power and precision by decreasing the variability of intrasubject response (Delfino et al., 2002).

14.5.5.1 Summary of Previous Assessments

Previous assessments have reviewed the weight of evidence from panel studies with respect to the health effects of PM exposures. Since the Government of Canada's last PM assessment, however, there is considerably greater panel study evidence of the health effects associated

with respiratory and cardiovascular endpoints, as well as of the biomarkers of inflammation and other health effect pathways.

All the panel studies reviewed in the 1999 PM SAD focused on the respiratory effects of air pollution, and most were conducted in children, with limited attention given to effects in older adults. Associations were documented between PM and small reversible decrements in lung function in healthy children, and in adults and children who had pre-existing respiratory conditions, particularly asthma. Other effects studied included increases in respiratory symptoms, and an increased number of lost work days and school absences.

The US EPA 2004 PM AQCD did not formally review all panel studies as a distinct group in one section of its document. Effects on respiratory endpoints were reported in subjects, including asthmatic children, and the effects were observed at long lags in some studies. In asthmatic subjects, PM was associated with declines in lung function, and less consistently with respiratory symptoms (cough, phlegm, difficulty breathing, bronchodilator use). Similar effects on respiratory symptoms were observed in non-asthmatic subjects. Alterations in haematological parameters (CRP, fibrinogen, blood viscosity) were observed in fewer studies. It was noted that PM was associated with declines in ECG markers of cardiac function (HRV) in several panels of older adults. While it was concluded that these results provided only very limited suggestive evidence of pathophysiological alterations that contribute to serious PM-related cardiovascular effects (MI, stroke, mortality), the breadth of changes was suggestive of a chain of endpoints linked to potential mechanisms of action for cardiovascular-related effects. It was concluded that further research was required to understand the relationships between exposure to ambient particles and more subtle endpoints.

14.5.5.2 Respiratory Effects

Although variable results exist, a link between exposure to air pollution and respiratory effects (including decrements in lung function) has been previously established. Much of the recent research (studies identified since those assessed in the US EPA 2004 PM AQCD) continues to focus on effects in young asthmatic subjects.

Personal PM_{2.5} has been associated, to various degrees, with respiratory outcomes in some studies of asthmatic children. In a group of 19 Californian asthmatic children, followed for 2 weeks in the spring or fall, significant associations were observed between personal PM_{2.5} (mean 24-h average: 33.4 µg/m³) and declines in FEV₁. The strongest association was for a 5-d moving average of 12-h daytime personal PM_{2.5} (-22% (95% CI -34% to -11%) per 40 µg/m³). Significant declines were also observed for other measures of personal PM_{2.5} (max 1-h, max 8-h, mean 12-h daytime, mean 12-h nighttime and mean 24-h) and at other lags (most consistently with the previous 24 h and a 4-d moving average). Significant declines in FEV₁ were also associated with indoor PM_{2.5} (last run day, 2- and 5-d moving averages), while local outdoor and central site ambient concentrations of PM_{2.5} were associated with significant declines for the 5-d moving average only (Delfino et al., 2004).

In a second study a nearly significant decline in FEV₁ was associated with mean daily personal exposure to ambient PM_{2.5} (6.38 ± 1.60 µg/m³) (derived using sulphate concentrations) in a panel of approximately 75 asthmatic schoolchildren in Denver, CO, followed over three consecutive winters (data from Rabinovitch et al., 2004). However, the effect of personal ambient PM_{2.5} on FEV₁ values (-2.2% (95% CI -4.3% to 0.0%)) was twice as large as that for ambient PM_{2.5} (mean concentration of 12.699 ± 6.426 µg/m³) at -1.0% (95% CI -2.0–0.0%) per a 10 µg/m³ increment of PM_{2.5} (Strand et al., 2006).

In a third study of 17 children with mild, persistent asthma, in Seattle, WA, who participated in one or more monitoring sessions of 5–10 d over 3 years, declines in FEV₁, PEF and MMEF

were non-significantly associated with personal PM_{2.5} (median 24-h level 11.3 µg/m³), except for a significant decline in PEF only in subjects not taking anti-inflammatory medication (-10.48 L/min (95% CI -18.68L/min to -2.28 L/min) per 10 µg/m³; p = 0.02 for medication status interaction). In this study stronger associations for all lung function measures were observed with indoor PM_{2.5} (Trenga et al., 2006).

In another Seattle study, stronger associations with decrements in lung function were observed with indoor-generated PM_{2.5} than ambient-generated PM_{2.5}. Ambient-generated and indoor-generated particles were differentiated using time–activity data, indoor and outdoor concentration data, and infiltration rates from a recursive mass balance model or a predictive model. The association was attributed in part to the fact that people spend so much of their time indoors. Mean 24-h PM_{2.5} values were 9.5 and 11.1 µg/m³ for indoor and outdoor (at home), respectively. Mean estimated indoor and outdoor generated PM_{2.5} values were 3.2 and 6.4 µg/m³, respectively. The study group comprised 19 asthmatic children, each followed for 10 d. A 10 µg/m³ increase in indoor, but not ambient-generated PM_{2.5} was associated with decreases in FEV₁ and FVC (p = 0.01 and p = 0.000, respectively, for indoor-generated PM_{2.5}; data not presented for ambient-generated PM_{2.5}) (Koenig et al., 2005).

No changes in respiratory effects were observed in other studies of asthmatic subjects using more traditional PM metrics. In wintertime panels of asthmatic children in Los Angeles, CA, (n = 22; daily diaries for up to 3 months) and Denver, CO, (three consecutive winters: n = 41 (year 1), n = 62 (year 2), and n = 43 (year 3)) declines in lung function were not associated with PM. In Los Angeles, declines in PEF were not significantly associated with lag 0 24-h average PM₁₀ (59.9 ± 24.7 µg/m³, -3.67 L/min (95% CI -10.3L/min to 2.91 L/min) per 37.0 µg/m³). Similar results were reported for EC and OC (24-h averages of 5.09 ± 1.86 µg/m³ and 9.47 ± 3.08 µg/m³, respectively) (Delfino et al., 2003). In Denver, CO, 24-h average PM₁₀ (28.1 ± 13.2 µg/m³) and PM_{2.5} (10.8 ± 7.1 µg/m³) were not significantly associated with morning or evening declines in FEV₁ with a 3-d moving average (all p-values >0.175) (Rabinovitch et al., 2004). While PM₁₀ was not associated with decrements in mean PEF, positive associations at lag 1 d and with a 5-d average were observed between PM₁₀ and PEF decreases 20% below the median in a study of British children with wheezing (n = 42) (OR = 1.030 (95% CI 1.001–1.060) and OR = 1.114 (95% CI 1.057–1.174), respectively). No significant declines in PEF were observed in all children combined (i.e. those with and without wheezing) (n = 177). Children were followed for 63 days and mean 24-h PM_{2.5} concentrations ranged from 18.4 ± 9.8 µg/m³ to 22.7 ± 10.6 µg/m³ (Peacock et al., 2003). Declines in FEV₁ or FVC were not significantly associated with 10 µg/m³ increments of 24-h PM_{2.5} (average: 27.2 ± 19.4 µg/m³) or PM₁₀ (average: 42.8 ± 21.8 µg/m³) in the only identified study of adult asthmatics (11 Italian subjects) who participated in two 1-month sessions in spring and winter. P-values ranged from 0.239 to 0.886 over lags 1–3 d (Lagorio et al., 2006).

In three other US studies of asthmatic children, positive associations between respiratory endpoints and air pollution were limited to or stronger in children taking medication (Gent et al., 2003; Delfino et al., 2003; Lewis et al., 2005), but in a fourth study, effects were only observed or were stronger in subjects not taking medication (Trenga et al., 2006).

In the first study, of 271 subjects in Massachusetts who participated in all or part of a 183-d sampling period, exposure to PM_{2.5} (mean 24-h average: 13.1 ± 7.9 µg/m³) was associated with chest tightness (lag 0 d), persistent cough (lag 1 d) and shortness of breath (lag 1 d). These effects were stronger in subjects taking maintenance medication (steroids, cromolyn sodium or leukotriene inhibitors) compared with those not on medication (p < 0.001) (Gent et al., 2003).

In the second study, 86 children, primarily African-American (>75% with persistent asthma) in Detroit, MI, were followed over six 2-week sessions throughout the winter and spring (average

daily mean $PM_{2.5}$: $15.7 \pm 10.6 \mu\text{g}/\text{m}^3$ (eastside), $17.5 \pm 12.2 \mu\text{g}/\text{m}^3$ (southwest); average daily mean PM_{10} : $23.0 \pm 13.5 \mu\text{g}/\text{m}^3$ (eastside), $28.2 \pm 16.1 \mu\text{g}/\text{m}^3$ (southwest)). In subjects taking corticosteroids, a $19.1 \mu\text{g}/\text{m}^3$ increment of PM_{10} was associated with increased diurnal variability FEV_1 and decreased lowest daily value FEV_1 at lag 2 d (5.32 mL (95% CI 0.32–10.33 mL) and -2.21 mL (95% CI -3.97 mL to -0.46 mL), respectively). When ozone was included in the model, even stronger associations were observed at lag 2 d (13.73 mL (95% CI 8.23–19.23 mL) and -5.97 mL (95% CI -11.06 mL to -0.87 mL), for diurnal variability FEV_1 and lowest daily value FEV_1 , respectively), as well as at lag 1 d for lowest daily value FEV_1 and lag 3–5 d for diurnal variability FEV_1 . No associations with $PM_{2.5}$ were observed in single-pollutant models, but in two-pollutant models with ozone increases in diurnal variability FEV_1 and decreases in lowest daily value FEV_1 were observed at lag 3–5 d (2.70 mL (95% CI 1.0–4.40 mL)) and -2.78 mL (95% CI -4.87 mL to -0.70 mL), respectively, per $12.5 \mu\text{g}/\text{m}^3$. In contrast to the results reported for children taking corticosteroids, few significant associations were observed in subjects not taking medication. Those that were reported were also smaller in magnitude (increased diurnal variability FEV_1 in two-pollutant models with ozone: 2.21 mL (95% CI 0.26–4.16 mL) and 2.92 mL (95% CI 0.74–5.11 mL), per increments of 12.5 and $19.1 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ and PM_{10} , respectively, for lag 3–5 d) (Lewis et al., 2005).

Delfino et al. (2003; study details presented earlier) observed that among California children, asthmatic children on anti-inflammatory medication (6 of 22 subjects taking corticosteroids or leukotriene inhibitors) had a higher response magnitude for asthma symptoms than those not on medication ($p < 0.07$) and were more likely to have more severe symptoms than those not on medication, although this increase was not significant ($p = 0.18$). In all subjects, associations were strongest at lag 0 d and diminished with increasing lag. In single-pollutant models PM_{10} , EC and OC were associated with increases in the likelihood of more severe asthma symptoms (symptom scores > 1) at lag 0 d (OR = 1.45 (95% CI 1.11–1.90) per $37 \mu\text{g}/\text{m}^3$ PM_{10} , OR = 1.85 (95% CI 1.11–3.08) per $2.91 \mu\text{g}/\text{m}^3$ EC, and OR = 1.88 (95% CI 1.12–3.17) per $4.64 \mu\text{g}/\text{m}^3$ OC). In two-pollutant models with PM_{10} and EC or OC, ORs for PM_{10} , but not EC or OC, decreased to near unity and all confidence intervals included unity. No significant interactions between these fractions and volatile organic compounds (VOCs) were observed in two-pollutant models. However, in these models, effect estimates for PM_{10} decreased much more than for VOCs, whereas with estimates for EC and OC the magnitude of decline was similar to that of VOCs when regressed together.

In contrast to the first three studies, Trenga et al. (2006) observed that $10 \mu\text{g}/\text{m}^3$ increments of $PM_{2.5}$ were associated with declines in FEV_1 , PEF and MMEF in 11 asthmatic Seattle, WA, children not taking anti-inflammatory medication. In total, 17 children participated in 26 monitoring sessions of 5–10 d each over 3 years. Median daily averages were 9.6, 11.2 and $7.5 \mu\text{g}/\text{m}^3$ for local outdoor, central site and indoor $PM_{2.5}$ concentrations. Declines in MMEF were associated with local outdoor $PM_{2.5}$ (-8.23 L/min (95% CI -14.77 L/min to -1.69 L/min)) and central site $PM_{2.5}$ (-8.21 L/min (95% CI -14.79 L/min to -1.62 L/min)) at lag 0 d. The p-values for medication status interaction were 0.0051 and 0.008, respectively (associations were non-significant in subjects taking medication). Indoor $PM_{2.5}$ was significantly associated at lag 0 d (for FEV_1 , PEF and MMEF) and lag 1 d (for PEF and MMEF) in subjects not taking anti-inflammatory medication, at lags 0 d and 1 d (for PEF) in subjects taking medication and in all subjects at lag 1 d (for MMEF).

It was hypothesized by some authors that more effects would be observed in asthmatic children taking medication, because medication use can be considered a surrogate for asthma severity (Lewis et al., 2005). Other authors suggested that medication use may dampen any potential effects of exposure to air pollution (Rabinovitch et al., 2004). Parental or subject intervention to

alleviate adverse effects or avoidance of environments that may promote adverse outcomes may also contribute to a lack of observed effects (Rabinovitch et al., 2004, 2006).

Effects on lung function have also been observed to be greater in asthmatic subjects with the presence of an upper respiratory infection. Among children reporting an upper respiratory infection in a study in Detroit, MI, declines in lowest daily value FEV₁ were associated with changes in PM_{2.5} (-2.88% (95% CI -5.46% to -0.30%) per 12.5 µg/m³) and PM₁₀ (-4.48% (95% CI -8.36% to -0.60%) per 19.1 µg/m³) for lag 3–5 d. The majority of associations in children without an upper respiratory infection were not significant (data not presented); PM₁₀ was associated with PEF at lag 1 d (OR = 1.72 (95% CI 0.38–3.06)). In separate two-pollutant models with ozone, PM_{2.5} and PM₁₀ were associated with declines in lowest daily value FEV₁ for lag 3–5 d (-2.78% (95% CI -4.79% to -0.77%) and -3.17% (95% CI -5.82% to -0.51%), respectively) in children with an upper respiratory infection. An association was also observed for PM₁₀ at lag 1 d (-13.11% (95% CI -21.59% to -4.62%). In both groups of children combined (with or without an upper respiratory infection), significant associations in two-pollutant models were observed between ozone but not PM₁₀ or PM_{2.5} and increases in diurnal variability FEV₁ (Lewis et al., 2005; study details presented earlier).

Medication use (as opposed to the influence of medication status) was a frequently studied endpoint in asthmatic children. In studies of asthmatic subjects the associations between bronchodilator use (e.g. albuterol) and PM were mixed. Using meta-analysis techniques to study daily diary card data from 990 children in eight North American cities (part of the 22-month pre-randomization phase of the Childhood Asthma Management Program (CAMP) study) it was concluded that there was no evidence for a year-round effect of PM₁₀ (24-h average concentrations ranged from 17.7 to 28.5 µg/m³) on rescue inhaler use, except for small increases when PM₁₀ was considered simultaneously with CO at lag 2 d (OR = 1.05 (95% CI 1.01–1.09) per 25 µg/m³). However, it is important to note that while PM₁₀ measurements were considered a primary source of data, >50% of PM₁₀ values in six of eight cities were modelled due to missing data. Significant single-pollutant results were reported for CO and NO₂ (Schildcrout et al., 2006).

Increased ambient PM was associated with bronchodilator use in a panel of 133 asthmatic children from Seattle who completed on average 58 daily diary cards as participants of the CAMP screening phase. PM_{2.5} and PM₁₀ (median 24-h concentrations were 7.3 and 21.0 µg/m³, respectively) were associated with increased inhaler use (RR = 1.08 (95% CI 1.01–1.15) per 10 µg/m³ PM_{2.5} at lag 1 d, and RR = 1.05 (95% CI 1.00–1.09) per 10 µg/m³ PM₁₀ at lag 0 d; RRs decreased and were not significant at longer lags). In two-pollutant models with CO these effects remained positive but were non-significant. Significant effects were also associated with CO in single-pollutant models (Slaughter et al., 2003). In mostly moderate-to-severe asthmatic children in Denver, CO, followed over one to three consecutive winters, PM₁₀ and PM_{2.5} were not associated with bronchodilator use (data not presented) (Rabinovitch et al., 2004; study details presented earlier). In similar children followed over one to two winters (n = 37 and n = 57 for each year) in the same city, hourly but not 24-h PM_{2.5} exposure was associated with bronchodilator use (3.8% (95% CI 0.2–7.4%) per 6.4 µg/m³ morning maximum PM_{2.5}) and this effect was stronger in severe asthmatics than in subjects with mild or moderate asthma (p = 0.03). Average daily concentrations of PM_{2.5} (TEOM) in the two years were 6.5 ± 3.2 µg/m³ and 8.2 ± 3.7 µg/m³. Daily 24-h PM₁₀ concentrations (not reported) were not associated with bronchodilator use (hourly effects not assessed). Daily averaged CO exposure (but not NO₂, SO₂ or O₃) was positively associated with medication use; gaseous pollutants were not tested at shorter lags (Rabinovitch et al., 2006). In an 11-month study of 148 Australian children, PM₁₀ (24-h average: 22.8 ± 13.8 µg/m³), CO and NO₂ were not associated with inhaler use (ORs for PM₁₀ at or near unity for all lags) in single-pollutant models. In a multi-pollutant model with all

three pollutants, inhaled corticosteroid use in subjects with wheeze was associated with PM₁₀ (OR = 1.27 (95% CI 1.08–1.49)) (Jalaludin et al., 2004).

Mar et al. (2004) observed associations, varying by PM fraction and age, in Seattle, WA, asthmatics followed for an average of 522 ± 181 d (16 adults) or 478 ± 17 d (9 children). Average PM levels over the 3 years of the study ranged from 6.9 ± 3.7 µg/m³ to 9.8 ± 5.3 µg/m³ for PM_{1.0}, from 8.1 ± 3.8 µg/m³ to 16.0 ± 5.9 µg/m³ for PM_{2.5} and from 16.8 ± 8.0 µg/m³ to 24.5 ± 18.5 µg/m³ for PM₁₀. In children, PM was positively associated with cough at lags 0, 1 or 2 d. At lag 0 d, OR = 1.09 (95% CI 1.02–1.16), OR = 1.17 (95% CI 0.98–1.40), OR = 1.07 (95% CI 0.96–1.20) and OR = 1.20 (95% CI 1.00–1.44) per 10 µg/m³ PM₁₀, PM_{2.5}, PM_{10–2.5} and PM₁, respectively. Runny nose was associated with PM₁₀ and PM_{10–2.5} at all lags, while marginally positive increases in sputum production were also associated with these two metrics. All fractions were associated with the general category “any symptoms,” and effects appeared to increase in line with a decrease in particle diameter, though this trend was not tested statistically (OR = 1.05 (95% CI 0.95–1.16); OR = 1.07 (95% CI 1.02–1.11); OR = 1.17 (95% CI 1.03–1.34); and OR = 1.18 (95% CI 1.04–1.33) per 10 µg/m³ increases of PM_{10–2.5}, PM₁₀, PM_{2.5} and PM₁, respectively, at lag 0 d). Similar effects were observed at lags 1 and 2 d. In contrast to the effects observed in children, no significant positive effects were observed in adults.

In an 11-month Australian study, children from Sydney with wheeze, positive histamine challenge and doctor-diagnosed asthma (n = 45) were not consistently more sensitive to the effects of air pollution on wheeze, cough, beta-2 agonist or corticosteroid use or doctors visits for asthma than children with wheeze only (n = 20) or children with wheeze and doctor-diagnosed asthma (n = 60). The authors concluded that no consistent adverse effects of air pollution were observed. Mean daytime PM₁₀ averaged 22.8 µg/m³ and PM₁₀ exposure was not associated with wheeze or cough in all children. The only positive findings were with doctor visits for asthma in all children (OR = 1.11 (95% CI 1.04–1.19) per 12.0 µg/m³ PM₁₀ at lag 0 d; similar effects were seen at lags 1 and 2 d and with 2- and 5-d moving averages). This association remained significant in multi-pollutant models with ozone and NO₂. Results from single-pollutant models for the different groups were not presented; and in multi-pollutant models (all three pollutants) the only significant association with PM₁₀ was for doctors' visits for asthma in subjects with wheeze (OR = 1.12 (95% CI 1.02–1.23)) (Jalaludin et al., 2004).

In another 2-month study designed to develop predictive models of asthma and rhinitis symptoms in 24 asthmatic subjects aged 9–64 years from Tulsa, OK, PM_{2.5} (24-h average: 13.07 µg/m³) was a much weaker and non-significant predictor of symptoms than ozone and pollen (Newhouse et al., 2004). In a third study of daily diary card data from the pre-randomization phase of the CAMP study, it was concluded that there was no evidence for a year-round effect of PM₁₀ on asthma symptoms, except for small increases when PM₁₀ was considered simultaneously with either CO or NO₂. In these two-pollutant models the ORs for asthma symptoms were 1.08 (95% CI 1.02–1.14) and 1.08 (95% CI 1.02–1.15) per 25 µg/m³ at lag 2 d, respectively. However, it is important to note that while PM₁₀ measurements were considered a primary source of data, more than 50% of PM₁₀ values in six of eight cities were modelled, due to missing data. Significant single-pollutant results were reported for CO and NO₂ (Schildcrout et al., 2006; study details presented earlier).

New studies provide limited evidence for an association with increased risk of serious asthma attacks or exacerbation of asthma. In asthmatic children from Seattle, WA, the odds of having a more severe asthma attack compared with a less severe one or no attack were significantly associated with PM₁₀ and PM_{2.5} (OR = 1.12 (95% CI 1.04–1.22) per 10 µg/m³ PM₁₀ at lag 0 d, and OR = 1.20 (95% CI 1.05–1.37) per 10 µg/m³ PM_{2.5} at lag 1 d). These effects remained after adjusting for the previous day's asthma or for CO in two-pollutant models (Slaughter et al., 2003; study details presented earlier). Neither PM_{2.5} or PM₁₀ were associated with asthma

exacerbation in a panel of asthmatic children in Denver, CO, (exacerbation defined as asthma episodes requiring oral prednisone use, visits to urgent care facilities, emergency departments or hospitalization) (Rabinovitch et al., 2004; study details presented earlier).

Varying degrees of reductions in lung function were observed in most of the recently identified studies of subjects with COPD. In the only Canadian study, 16 subjects with COPD in Vancouver, BC, were monitored for 24 h over five to seven sessions. Significant declines in delta-FEV₁ were associated with estimated exposures to ambient PM_{10-2.5}, PM_{2.5} and nonsulphate PM_{2.5} (-38.20 mL (95% CI -57.32 mL to -19.07mL) per a 2.4 µg/m³ increment, -28.93 mL (95% CI -54.55 mL to -3.30 mL) per a 4.4 µg/m³ increment, and -30.43 mL (95% CI -55.02 mL to -5.84 mL) per a 3.4 µg/m³ increment, respectively), but not with ambient concentrations of PM₁₀, PM_{2.5} or PM_{10-2.5} (non-significant declines with wide confidence intervals). No significant declines were observed when only post-sample FEV₁ values were considered; a significant increase was observed with estimated exposure to non-ambient PM_{2.5}. Measured concentrations of 24-h averaged ambient PM₁₀, ambient PM_{2.5} and total personal exposure to PM_{2.5} were 17 ± 6 µg/m³, 11.4 ± 4.6 µg/m³, and 18.5 ± 14.9 µg/m³, respectively. Estimated exposures to ambient PM₁₀ and PM_{2.5} were 10.3 ± 4.6 µg/m³ and 7.9 ± 3.7 µg/m³ (Ebelt et al., 2005).

In another study the associations of PM₁₀ and PM_{2.5} with lung function decrements increased with longer lags (24-h, 48-h and 72-h moving averages) in 11 Italian subjects with COPD. With a 72-h moving average, significant declines were associated with 10 µg/m³ increments of PM₁₀ (-0.94% FVC, p = 0.045; and -0.87% FEV₁, p = 0.1040) and PM_{2.5} (-1.10% FVC, p = 0.044; and -1.06% FEV₁, p = 0.032). Declines in lung function were also associated with Zn, Cr, Fe and Ni components of PM_{2.5}; the authors attributed Zn and Fe to traffic-related components (Lagorio et al., 2006; study details presented earlier in this section).

In 24 older adult subjects with and without COPD in Seattle, WA (one or more monitoring sessions of 5–10 d each over 3 years) decreases in FEV₁ in all subjects were significantly associated with a 10 µg/m³ change in central site PM_{2.5} (24-h average: 10.3 µg/m³) at lag 0 d (-35.5 mL (95% CI -70.0 mL to -1.0 mL) and lag 1 d (-40.4 mL (95% CI -71.1 mL to -9.6 mL). When stratified by the presence of COPD, declines in FEV₁ were observed in both groups at both lags, but the effect was only significant at lag 1 d in subjects with COPD (-70.8 mL (95% CI -118.4 mL to -23.1 mL)). No changes in lung function (FEV₁ or PEF) were associated with outdoor, indoor or personal measures of PM_{2.5}, which were all slightly lower than central site monitoring values. In addition, no changes in SpO₂ were associated with PM (Trenga et al., 2006).

In other studies PM was not associated with changes in respiratory endpoints in subjects with COPD. In a Seattle study of subjects with COPD, asthma or both, followed for 12 d, no changes in spirometry, SpO₂ or pulse rate were associated with PM₁₀, PM_{2.5} or BC (mean central site 24-h averages of 18, 14 and 7.2 µg/m³, respectively) in the four subjects with COPD (Jansen et al., 2005). In a study of two panels (n = 16, n = 18, followed over two consecutive winters in Denver, CO), with varying severities of COPD, changes in FEV₁ and PEF were often in unexpected directions; the only significant decline in lung function was a decrease in PEF associated with PM₁₀ at lag 2 d in the second panel (p < 0.05). Concentrations of PM₁₀ and PM_{2.5} were slightly higher in the second year than the first (25.1 ± 12.3 µg/m³ and 9.0 ± 5.2 µg/m³, and 29.6 ± 13.8 µg/m³ and 14.3 ± 9.6 µg/m³ for the first and second panel, respectively). No PM₁₀- or PM_{2.5}-related changes in medication use, symptoms, or exacerbation of COPD were observed in this study (Silkoff et al., 2005) or an earlier 13-month Parisian study of 39 subjects with COPD at similar PM₁₀ concentrations (Desqueyroux et al., 2002).

Studies in other potentially susceptible subpopulations are limited. Fine PM was not associated with changes in lung function in seven subjects with IHD in Rome, Italy (Lagorio et al., 2006; study details presented earlier in this section). In groups of European older adults with CHD from three centres—Erfurt, Germany (n = 47); Amsterdam, the Netherlands (n = 37); Helsinki, Finland (n = 37)—followed over 6 months, it was observed that increases in cardiorespiratory symptoms (e.g., shortness of breath, phlegm and prevalence of being awakened by breathing problems) were more strongly associated with PM_{2.5} than with NC_{0.01–0.1} or PM₁₀, although at some lags many of the associations with PM_{2.5} were only marginally positive. Significant results were reported for a 10 µg/m³ increment of PM_{2.5}: prevalence of shortness of breath at lag 3 d (OR = 1.12 (95% CI 1.07–1.17)), as well as prevalence of being awakened by breathing problems at lag 1 d (OR = 1.10 (95% CI 1.03–1.17)) and with a 5-d average (OR = 1.14 (95% CI 1.03–1.25)). Significant associations were also observed with a 10,000 n/cm³ increment of NC_{0.01–0.1}: prevalence of being awakened by breathing problems at lag 3 d (OR = 1.08 (95% CI 1.01–1.15)), as well as prevalence of avoidance of activities at lag 0 d (OR = 1.10 (95% CI 1.01–1.19)) and with a 5-d average (OR = 1.19 (95% CI 1.01–1.142)). Results for PM₁₀ were not presented. In general, associations with symptom incidence appeared slightly greater than with symptom prevalence, although many results did not reach statistical significance. The average ranges of 24-h mean concentrations across the three centres were approximately 20–35 µg/m³, 10–20 µg/m³ and 17,000–21,000 n/cm³ for PM₁₀, PM_{2.5} and NC_{0.01–0.1}, respectively. No associations were observed with CO or NO₂ (de Hartog et al., 2003).

Older Dutch adults from urban and rural areas (followed over two consecutive winters) who were IgE+/AHR+ were more susceptible to the effects of 10 µg/m³ increases in PM₁₀ (average 24-h mean: ~ 25–45 µg/m³) and BS (average 24-h mean: ~10–25 µg/m³) at lags 0, 1 and 2 d and with a 5-d mean as compared with subjects with other IgE and AHR statuses. The effects were seen on PEF, cough and upper respiratory symptoms (URS). For both sexes combined, positive effects were observed with both pollutants, although significance was only observed with BS (URS: OR = 1.19 (95% CI 1.06–1.33) for a 5-d mean; >10% change in PEF: OR = 1.16 (95% CI 1.04–1.29) for a 5-d mean; cough: OR = 1.08 (95% CI 1.02–1.14) at lag 0 d). Declines in lung function were stronger, positive, and significant only in females (OR = 1.12 (95% CI 1.01–1.24) at lag 0 d). However, effects on symptoms were positive in both sexes, but only significant in males (URS: OR = 1.06 (95% CI 1.02–1.10) at lag 2 d of PM₁₀; and OR = 1.43 (95% CI 1.20–1.69) for a 5-d mean of BS; cough: OR = 1.16 (95% CI 1.05–1.29) for a 5-d mean of BS). Effects were also associated with exposure to NO₂ or SO₂ (Boezen et al., 2005). In a 3-year panel study of 88 Seattle, WA, subjects with CVD or COPD, no associations between personal, indoor or local outdoor PM_{2.5} or PM₁₀ and SpO₂ were observed (data not presented). Average daily personal, indoor, and local outdoor concentrations of PM_{2.5} were 10.8 ± 8.4, 9.5 ± 6.8, and 12.6 ± 7.9 µg/m³ in subjects with CVD, and 10.5 ± 7.2, 8.5 ± 5.1, and 9.2 ± 5.1 µg/m³ in subjects with COPD. Indoor and local outdoor concentrations of PM₁₀ were 16.2 ± 11.3 and 18.0 ± 9.0 for the CVD group, and 14.1 ± 6.6 and 14.3 ± 6.8 µg/m³ for the COPD group (Mar et al., 2005a).

A limited number of studies with mixed results were conducted with healthy subjects. Decreases in lung function and increases in respiratory symptoms were associated with PM in Austrian schoolchildren. In one study of 56 children who participated in one or more measurements per week, daily mean active particle surface (57.46 ± 25.25 µm²/cm³; increment not reported) was associated with declines in FVC (p = 0.006), FEV₁ (p = 0.001) and increases in wheezing (p = 0.001), shortness of breath (p = 0.041) and cough (p = 0.041 and p = 0.031 for evening and night cough, respectively) (Moshhammer and Neuberger, 2003). In a second study, 163 schoolchildren participated in biweekly measurements for approximately 9 months. Median 24-h mean concentrations of PM₁₀, PM_{2.5} and PM₁ were 25.73, 15.79 and 13.20 µg/m³, respectively. Changes of 10 µg/m³ in each of these fractions were associated with declines in FEV₁, FEV_{0.5},

MEF_{75%}, MEF_{50%}, MEF_{25%}, PEF and R(0,c) ($p < 0.05$ for all estimates) (Moshhammer et al., 2006). Finally, data collected for all four seasons from children in urban and rural areas (approximately 458–621 per season) suggested that PM₁ and PM_{2.5} were associated with increased respiratory problems and declines in lung function; pollutant data were not reported (Neuberger et al., 2004). In the only study to include multi-pollutant models the most stable significant declines in lung function were associated with NO₂; the only PM_{2.5} effect that remained positive was an influence on peripheral airway resistance measured using the impulse oscillation system (R(0,c) (hypothetical resistance at frequency = 0)) ($p = 0.004$) (Moshhammer et al., 2006).

No declines in lung function were associated with PM₁₀ or BS (p -values > 0.05) in 68 Dutch children followed for 7 weeks, during which time average mean PM₁₀ and BS levels were 56 and 20 $\mu\text{g}/\text{m}^3$, respectively (Fischer et al., 2002). In 46 healthy Parisian adults followed for 14 weeks, increases in respiratory symptoms were significantly associated with BS and PM₁₀ (daily means averaged 19.3 ± 16.1 and 24.2 ± 12.3 $\mu\text{g}/\text{m}^3$, respectively). A 14.1 $\mu\text{g}/\text{m}^3$ increment of PM₁₀ was associated with clear rhinorrhea and cough (OR = 1.51 (95% CI 1.16–1.97) and OR = 1.35 (95% CI 1.01–1.81), respectively) as well as “group of symptoms of any type” (OR = 1.37 (95% CI 1.04–1.80)). Similar, but slightly weaker associations were observed with BS, in addition to associations with headache and the group of “possible infection” symptoms. No associations with declines in PEF were observed (Segala et al., 2004). Declines in lung function were not associated with PM_{2.5} (p -values > 0.05) in 354 day hikers observed pre- and post-hike in Great Smoky Mountains National Park, USA. The estimated mean exposure to PM_{2.5} was 15.0 ± 7.4 $\mu\text{g}/\text{m}^3$ (Girardot et al., 2006). In 28 healthy, older adults living in Boston, MA, decreases in SpO₂ at rest were associated with 6-h lag PM_{2.5} in all subjects pooled (-0.172% (95% CI -0.313% to -0.031%) per 11.45 $\mu\text{g}/\text{m}^3$ hourly PM_{2.5}) and subjects taking beta-blockers ($n = 5$), all of whom had higher blood pressure (-0.769% (95% CI -1.21% to -0.327%) per 13.42 $\mu\text{g}/\text{m}^3$ PM_{2.5}), but not in subjects not taking beta-blockers (-0.062% ; 95% CI -0.248 – -0.123%) per 13.42 $\mu\text{g}/\text{m}^3$ PM_{2.5}). Local ambient concentrations of PM_{2.5} were not reported (DeMeo et al., 2004). Finally, personal, indoor or local outdoor PM_{2.5} (24-h averages of 9.3 ± 8.4 , 7.4 ± 4.8 and 9.0 ± 4.6 $\mu\text{g}/\text{m}^3$, respectively) and indoor or local outdoor PM₁₀ (24-h averages of 12.6 ± 7.8 and 14.5 ± 7.0 $\mu\text{g}/\text{m}^3$, respectively) were not associated with SpO₂ in healthy older adults followed for 3 years in Seattle, WA (data not presented) (Mar et al., 2005a).

One study is reviewed here because of similarity in endpoints, not study design. Kulkarni et al. (2006) used sputum induction to determine the level of carbon in airway macrophages. Lung function and carbon content of macrophages were measured in 114 healthy and 9 asthmatic children in Leicestershire, UK, and compared with modelled annual PM₁₀ concentrations from hourly traffic emissions that were estimated at less than 2 $\mu\text{g}/\text{m}^3$. A 1 $\mu\text{g}/\text{m}^3$ increase in modelled annual PM₁₀ from road traffic was associated with the carbon content of macrophages (0.10 μm^2 ; 95% CI 0.01 – 0.18 μm^2), which was in turn dose-dependently associated with significant declines in FEV₁, FVC, FEF_{25–75} (-17% (95% CI -5.6% to -28.4%), -12.9% (95% CI -0.9% to -24.8%) and -34.7% (95% CI -11.3% to -58.1%) per a 1 μm^2 increment of carbon content, respectively) in healthy children. These effects remained significant after adjusting for the carbon content of PM₁₀. Comparisons between healthy and asthmatic children were made difficult by the fact that macrophage carbon content was not detected in eight of nine asthmatic subjects. The authors noted that it was unclear whether the association between lung function and carbon content of macrophages was a short- or long-term effect.

In several other panel studies PM was related to symptomatic outcomes or lung function in healthy and compromised subjects. Quantitative analyses were limited in three European studies (Steenenbergh et al., 2003; Ranzi et al., 2004; Lubinski et al., 2005). Pollutant concentrations in studies not conducted in Canada, the US or Europe were much greater than

ambient levels in Canada; these studies were judged to be less relevant to a Canadian assessment (Romieu et al., 2002, 2006; Sanchez-Carrillo et al., 2003 (acute cross-sectional study); Aekplakorn et al., 2003a; Pino et al., 2004; Preutthipan et al., 2004; Sharma et al., 2004; Park JW et al., 2005; Peled et al., 2005; Kim JH et al., 2005; Chan and Wu, 2005; Kasamatsu et al., 2006; Kongtip et al., 2006). The purpose of one Australian study was to investigate the health effects of vegetation fires in the monsoon tropics; this study was also deemed less relevant to exposures of the general Canadian population (Johnston et al., 2006). In only one identified study were no effects observed (Aekplakorn et al., 2003b). In a cross-sectional study in Taiwan, where annual average PM₁₀ values ranged from 54.1 to 84.3 µg/m³, no associations with lung function or asthma prevalence were observed in approximately 13,000 adolescent asthmatics (Kuo et al., 2002).

14.5.5.3 Effects on Biological Markers

Biological markers of effects are quantifiable parameters that are indicative of changes to biological systems. They help to identify the pathways and mechanisms by which air pollutants may challenge the body's biological systems. The utility of biomarkers is hindered by their lack of specificity, as the mechanisms of particle toxicity overlap with those of other substances. Another issue is the sensitivity of markers to detect very subtle changes induced by particles. Nevertheless, attempts have been made to identify biological markers of effects.

The most studied marker in the recent literature (published since the cut-off date for the US EPA 2004 PM AQCD) was fraction of exhaled nitric oxide (FeNO), a sensitive marker of airway inflammation. Elevated levels of FeNO (~4–5 ppb) were associated with 10 µg/m³ increments of PM₁₀ (6.5% (95% CI 0.9–12.4%)) and BS (31.1% (95% CI 7.4–60.2%)) at lag 1 d in 68 healthy Dutch children who were assessed once a week for 7 weeks. Mean 24-h averages of PM₁₀ and BS were 56 and 20 µg/m³, respectively. Similar findings were also observed with NO₂, NO and CO at lag 2 d (Fischer et al., 2002).

In another study, similar elevated levels of FeNO were also observed with 10 µg/m³ increments of personal, indoor, outdoor and central site PM_{2.5} (concentrations were all <15 µg/m³) at lag 0 d in 19 asthmatic children from Seattle, WA, not taking inhaled corticosteroids (4.5 ppb (95% CI 1.02–7.9 ppb), 4.2 ppb (95% CI 1.02–7.4 ppb), 4.3 ppb (95% CI 1.4–7.29 ppb) and 3.8 ppb (95% CI 1.2–6.4 ppb) respectively). No effects were observed in subjects taking corticosteroids. Subjects participated in 10-d monitoring sessions in spring and/or winter (Koenig et al., 2003). When these exposures were analyzed as indoor vs. ambient generated PM_{2.5}, elevated FeNO was only associated with a 10 µg/m³ increase in ambient generated PM_{2.5} (5.0 ppb (95% CI 0.3–9.7 ppb)) (Koenig et al., 2005). In addition, these data were analyzed at shorter lags, and associations between 10 µg/m³ hourly PM_{2.5} and FeNO were observed at lags 1 and 4 h using a linear effects model (6.9 ppb (95% CI 3.4–10.6ppb) and 6.3 ppb (95% CI 2.6–9.9 ppb), respectively). A trend of declining FeNO values was observed from approximately lag 0 to lag 12 h in both a polynomial distributed model and a GEE model controlling for autocorrelation (Mar et al., 2005b).

In 45 asthmatic adolescents from two centres in Southern California followed for 10 d each, smaller increases (<2 ppb) in FeNO were observed, using 2-d moving averages of personal PM_{2.5}, EC or NO₂. Generally stronger associations were observed for central site EC and NO₂ than PM_{2.5} at lag 1 d and with a 2-d moving average. Personal 24-h average PM_{2.5}, EC and OC concentrations, respectively, were 32.78 ± 21.84 µg/m³, 0.42 ± 0.69 µg/m³ and 5.63 ± 2.59 µg/m³ for Riverside and 36.2 ± 25.46 µg/m³, 0.78 ± 1.42 µg/m³ and 6.81 ± 3.45 µg/m³ for Whittier. Central site concentrations of PM_{2.5} were 36.63 ± 23.46 µg/m³ and 18 ± 12.14 µg/m³ for each centre, respectively. In contrast to the results from the studies in Seattle presented above, these effects were only significant in subjects taking anti-inflammatory medication or inhaled

corticosteroids, when data were stratified by medication use. In subjects taking anti-inflammatory medication, 2-d moving average increments of personal PM_{2.5} (2.4 µg/m³), EC (0.6 µg/m³), and OC (4.1 µg/m³) and increments of central site EC (0.8 µg/m³), and OC (2.9 µg/m³) were associated with increases in FeNO of 1.01 ppb (95% CI 0.19–1.84 ppb), 0.71 ppb (95% CI 0.28–1.15 ppb), 0.87 ppb (95% CI -0.79–2.53 ppb), 1.42 ppb (95% CI 0.25–2.60 ppb) and 2.05 ppb (95% CI 0.24–3.86 ppb), respectively. For subjects taking inhaled corticosteroids, associations with increments of personal PM_{2.5}, EC and OC and central site PM_{2.5} (15 µg/m³), EC and OC were 1.58 ppb (95% CI 0.72–2.43 ppb), 0.67 ppb (95% CI 0.28–1.07 ppb) and 2.47 ppb (95% CI 0.30–4.64 ppb), 1.16 ppb (95% CI 0.11–2.20 ppb), 1.28 ppb (95% CI 0.07–2.49 ppb) and 1.96 ppb (95% CI 0.14–0.035 ppb), respectively. Changes in central site PM₁₀ were not associated with elevated FeNO levels (data not presented) (Delfino et al., 2006).

In seven older adult asthmatic subjects (average age, 75) in Seattle, WA, increases in FeNO were significantly associated with increments of 10 µg/m³ local ambient PM_{2.5} or PM₁₀ and a 1 µg/m³ increment of BC (daily average concentrations of 8.99, 11.86 and 1.83 µg/m³, respectively). The increases in FeNO were 4.23 ppb (95% CI 1.33–7.13 ppb), 5.87 ppb (95% CI 2.87–8.88 ppb) and 2.32 ppb (95% CI 1.08–3.57 ppb), respectively. Significant positive associations were also observed with indoor and personal BC (Jansen et al., 2005). However, in another study of 11 slightly younger asthmatic subjects (41 ± 14 years of age) in Rome, Italy, no associations between FeNO and PM_{2.5} or any gaseous pollutant (NO₂, CO, SO₂, O₃) were observed (data not presented) (Lagorio et al., 2006; study details presented in Section 14.5.3.2).

In subjects with COPD, conflicting results were reported. In a 12-week study of 29 older adults from Steubenville, OH, who had COPD or COPD and asthma, or who were healthy, stronger effects were observed in the first two groups than in the healthy subjects (data not presented). In all subjects combined, there was an association between elevated FeNO levels and PM_{2.5} (24-h average: 19.7 µg/m³) in single-pollutant models (1.45 ppb (95% CI 0.33–2.57 ppb) for a 17.7 µg/m³ increase in the 24-h moving average of PM_{2.5} and 1.36 ppb (95% CI 0.58–2.14 ppb) for a 17.9 µg/m³ increase in current hour PM_{2.5}) and similar results in multi-pollutant models with ambient NO and room NO. Significant associations were also observed at lags 1, 2, 4, 6, 8, 10 and 12 h. While effect estimates were higher in subjects with COPD or COPD and asthma than in healthy subjects, heterogeneity still remained, suggesting the underlying disease state was not the only factor contributing to the variability in results. Increased FeNO was also related to NO, but not NO₂, O₃ and SO₂ (Adamkiewicz et al., 2004). By contrast, in a study of Seattle, WA, subjects, no associations between FeNO and indoor, ambient or personal PM₁₀, PM_{2.5} or BC were observed (Jansen et al., 2005; study details presented in Section 14.5.3.2).

Other markers have been studied much less in a range of different subjects. In 68 healthy adult Danish subjects who participated in four 2-d sessions, one in each season, personal exposures to PM_{2.5} (median: 16.1 µg/m³) were significantly associated with changes in levels of malondialdehyde (MDA, a measure of lipid peroxidation), RBC and haemoglobin, but only in female subjects (a 10 µg/m³ increase in PM_{2.5} was associated with increases of 3.7% (p-value not reported), 2.3% (p = 0.0009) and 2.6% (p = 0.003), respectively). Personal exposure to BC (median: 8.1 × 10⁻⁶/m) was associated with a significant increase in plasma proteins in all subjects (4.1% (p = 0.009) per 10⁻⁵/m BC), an effect that was only marginally associated with personal PM_{2.5} (p = 0.061) (Sørensen et al., 2003a, 2003b). In an analysis of data from 88 healthy older adults from three communities in Utah who participated in approximately three 24-h monitoring sessions, Pope et al. (2004a) observed a significant increase in CRP associated with 100 µg/m³ PM_{2.5} (0.81 (SE 0.17) mg/dL); however, with the exclusion of the most influential subject this relationship decreased four-fold (0.19 (SE 0.10) mg/dL; p < 0.10). In this study there were no associations with whole-blood viscosity, platelets or other cell counts. The average 24-

h mean PM_{2.5} concentration was 23.7 ± 20.2 µg/m³. Increases in urinary leukotriene E4, another marker of inflammation, were associated with morning maximum (6.2% (95% CI 1.9–10.5%) per 12 µg/m³ PM_{2.5}) but not daily average PM_{2.5} after controlling for upper respiratory infections in primarily moderately-to-severely asthmatic children taking controller medication in Denver, CO (Rabinovitch et al., 2006; study details presented in Section 14.5.5.2).

Stronger effects have been observed in subjects with a pre-existing disease, including subjects with diabetes, obesity and chronic heart disease. In the ULTRA (Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air) study (subjects with CHD in three European centres followed for 6 months) urinary CC16 (a protein specific to the lung epithelium secreted in the respiratory tract by nonciliated Clara cells; a marker of lung injury) levels were significantly associated with a 10 µg/m³ increase in PM_{2.5} (24-h average: 12.7 µg/m³) and a 1,000 n/cm³ increase in NC_{0.1–1} (24-h average: 1,390 n/cm³) only in Helsinki, Finland. Associations with PM_{2.5} were observed at lag 2 d (20.2% (95% CI 6.9–33.5%)), while significant associations with NC_{0.1–1} were observed at lags 0 and 3 d and with a 5-d mean (15.5% (95% CI 0.001–30.9%), 17.4% (95% CI 3.4–31.4%), and 43.2% (95% CI 17.4–69.0%), respectively). In further analyses the association with PM_{2.5} was more pronounced in male subjects (30.6% (95% CI 14.2–47.0%)), ex-smokers (30.6% (95% CI 14.1–47.1%)) and subjects with a chronic respiratory disorder (27.9% (95% CI 11.9–43.9%)) with similar significant effects at lag 0 d, lag 3 d and the 5-d mean. No effects were associated with exposure to UFPs. Analyses using two-pollutant models with the addition of CO, NO₂, NC_{0.01–0.1} or O₃ had little effect on single-pollutant model estimates for PM_{2.5} (Timonen et al., 2004).

Subjects with diabetes, obesity and hypertension were also identified as sensitive subgroups in a study of 44 older adults in St. Louis, MI, who participated in four monthly group trips on a diesel-powered shuttle bus. In this study the critical averaging period for effects on CRP, IL-6 and WBC levels was days, not hours. While the strongest associations were with central site PM_{2.5}, some of these endpoints were also related to microenvironmental PM_{2.5} and BC (daily averages of 16 ± 6.0 µg/m³, 9.8 ± 4.5 µg/m³ and 0.900 ± 280 µg/m³, respectively), as well as NO₂, CO and O₃. For all subjects combined, a 5.4 µg/m³ increase in PM_{2.5} over the previous week was associated with elevated WBCs (5.5% (95% CI 0.10–11%)), but no significant results were observed with CRP or IL-6. In subjects with diabetes, the 5-d mean PM_{2.5} was associated with CRP (74% (95% CI 18–158%) per 6.1 µg/m³); significant, positive results were also observed in obese subjects (48% (95% CI 5.3–109%)) and similar or weaker findings at other lags or moving averages. In subjects with diabetes, obesity and hypertension, this value increased to 81% (95% CI 21–172%). Elevated, but non-significant associations with IL-6 were observed in these subsets of subjects. Effect modification by disease status did not alter WBC counts and no effect modification was observed in subjects with hypertension. Elevated associations were observed in subjects with higher mean levels of inflammatory markers. In the top 25th percentile, PM_{2.5} was associated with increases in IL-6, CRP and WBCs for moving averages over 1–7 d, whereas no effects were observed for the lower 75th percentile of subjects (Dubowsky et al., 2006).

Two studies investigated changes in a variety of markers: one in older male subjects with CHD and one in healthy male state troopers. The biomarkers affected by various PM metrics (PM_{2.5}, EC, OC, AMPs and UFPs) in males with CHD (Rückerl et al., 2006) are linked to CVD (e.g. CRP (inflammation), factor VII (FVII) and prothrombins (both coagulation cascade), vWf (platelet adhesion) and ICAM-1 (endothelial dysfunction)). Changes in some of these same endpoints (CRP, vWf) were also observed in younger, healthy, male North Carolina state troopers (Riediker et al., 2004a). While the particle fractions and lag structures associated with these changes differed between the two studies, both sets of authors indicated that there was evidence for an effect of PM on inflammation and coagulation pathways; however, data on the

effects of PM on coagulation pathways were less consistent (Rückerl et al., 2006). In addition, through different mechanisms, both teams proposed that accumulation mode and traffic-related particles may be central to the effects observed in their respective studies. Finally, results from both groups suggested that different particles, based on fraction or composition, may act via different mechanisms of action.

In the study of older male subjects who participated in 12 clinical visits over 6 months (Rückerl et al., 2006) average 24-h mean concentrations of UFPs, AMPs, PM_{2.5} and PM₁₀ were 12,602 ± 6,455 n/cm³, 1,593 ± 1,034 n/cm³, 20.0 ± 15.0 µg/m³ and 20.0 ± 13.0 µg/m³, respectively. Increases in CRP above the 90th percentile were associated with PM₁₀, AMPs and UFPs at lag 2 d (OR = 2.2 (95% CI 1.2–3.8) per a 15.2 µg/m³ increment, OR = 3.2 (95% CI 1.7–6.0) per a 1,299 n/cm³ increment and OR = 2.3 (95% CI 1.3–3.8) per a 10,005 n/cm³ increment, respectively), as well as at lag 1 d and with a 5-d moving average of PM₁₀, but no associations were observed in linear models (data not presented). Declines in FVII were associated with 5-d moving averages of PM₁₀ (-8.0% (95% CI -12.4% to -3.4%) per 12.8 µg/m³), PM_{2.5} (-3.5% (95% CI -6.4% to -0.4%) per 12.2 µg/m³), AMPs (-4.1% (95% CI -7.9% to -0.3%) per 1,127 n/cm³) and UFPs (-6.6% (95% CI -10.7% to -2.3%) per 6,821 n/cm³) as well as at other lags with specific fractions; similar results were reported for changes >90th percentile (data not presented). While all fractions of PM were associated with vWF in linear models, there were more reports of non-linearity at specific lags for different fractions; however, several significant increases were reported for a 5-d average (for PM_{2.5}, 5.6% (95% CI 0.5–10.8%); for AMPs, 13.5% (95% CI 6.3–20.6%); and for UFPs, 7.8% (95% CI 1.4–14.3%) and at lag 1 d for PM₁₀ (6.0% (95% CI 0.6–11.5%)). All fractions were associated, to varying degrees, with increases in ICAM-1 above the 90th percentile (PM₁₀: OR = 3.4 (95% CI 2.2–5.2) at lag 2 d; PM_{2.5}: OR = 1.8 (95% CI 1.2–2.7) at lag 2 d; AMPs: OR = 1.8 (95% CI 1.2–2.8) at lag 1 d; and UFPs: OR = 0.6 (95% CI 0.4–1.0) at lag 0 d). Results for other biomarkers included increases in prothrombin 1+2 and serum amyloid A (SAA) greater than the 90th percentile across all pollutants at lag 4 d, and few or no changes in E-selectin (increases and decreases), D-dimer (estimates near unity) and fibrinogen (generally declines). Sensitivity analyses indicated that the effects observed in linear models were mostly driven by subjects not on lipid-lowering medication, but that when CRP data were stratified, effects were strongest for patients on statins (data not presented). Both EC and OC were significantly associated with declines in FVII and increases in vWF and ICAM-1; some associations with CO and NO₂ were also observed.

In the second study of nine younger state troopers followed for 4 consecutive days (Riediker et al., 2004a), a stronger influence of in-vehicle PM_{2.5} mass (daily average: 23.0 µg/m³) was observed compared with PM_{2.5}Lightscatter (daily average: 24.1 µg/m³) (the opposite trend was observed for HRV variables), indicating a role for AMPs (0.1–1.0 µm). Significant associations were observed between increases in CRP and vWf, and in-vehicle PM_{2.5} mass (31.9% (p < 0.023) and 1.8% (p < 0.018) per 10 µg/m³, respectively), as well as increases in RBC volume (0.9% (p < 0.045)) and percentage of neutrophils (6.2% (p < 0.036)), and decreases in percentage of lymphocytes (-10.5% (p < 0.025)). Associations with ambient PM_{2.5} and roadside PM_{2.5} (daily averages of 32.3 and 32.1 µg/m³, respectively) were generally lower than those from in-vehicle levels (no numerical estimates were given).

Several cross-sectional studies that used subsets of subject data from larger longitudinal studies investigated endpoints similar to those in the panel studies reviewed here. Results from the study of subjects who participated in the Atherosclerosis Risk in Communities (ARIC) Study, the VA Normative Aging Study and the Multi-ethnic Study of Atherosclerosis (MESA) research provided further evidence for the health effects of PM. Among subjects from the first study a 12.8 µg/m³ increase in PM₁₀ was associated with increases in vWf in diabetics (3.93% (SE 1.80); p < 0.05) and decreases in serum albumin in those subjects with a history of CVD (-0.006

g/dL (SE 0.003); $p < 0.05$). The association between PM_{10} and FVII was observed to be U-shaped, and, as put forward by the authors, suggestive of a threshold effect. Effects were also associated with exposure to O_3 , CO and SO_2 (Liao et al., 2005).

In subjects from the VA Normative Aging Study, a longitudinal study of aging in initially healthy, older adults, Zeka et al. (2006b) observed significantly elevated fibrinogen levels (a blood clotting factor) and an increase in sediment rate (a marker of inflammation) with 4-h, 1-week and 4-week moving averages of PN (24-h average: $27,160 \pm 15,851$ n/cm³) and BC (24-h average: 0.77 ± 0.63 ng/m³). Increases in fibrinogen were associated with a 15,851 n/cm³ change in PN (4.19% (95% CI 2.04–6.34%) and 2.14% (95% CI 0.05–4.23%) for 48-h and 1-week moving averages, respectively) and a 0.63 ng/m³ change in BC (1.78% (95% CI 0.19–3.36%) for a 4-week moving average). Significant associations with sediment rate for each pollutant were only observed with a 4-week moving average (43.65% (95% CI 15.47–71.83%); and 21.65% (95% CI 1.48–41.82%) for PN and BC, respectively). Associations with $PM_{2.5}$ (24-h average: 11.16 ± 7.94 µg/m³) were weaker and only significant for sediment rate (24.93% (95% CI 0.58–49.18%) per 7.95 µg/m³ with a 4-week moving average), and associations with sulphates were only suggestive. Analyses of effect modification provided suggestive, but non-significant, evidence that age, high BMI, a GSTM1 *null* genotype and non-use of statins may contribute to increased levels of these markers. Overall, the authors concluded that their results suggested traffic-related particles (PN, BC) have a higher toxicity than other particles ($PM_{2.5}$, sulphates).

In subjects who participated in the nation-wide American MESA study, no significant positive associations between CRP and $PM_{2.5}$ were observed in over 5000 healthy subjects in eight US centres at multiple lags (1–60 d) in multiple analyses (linear; logistic; stratified by season, age, sex, race/ethnicity, education, self-reported health or pre-existing conditions; stratified by other factors that affect CRP; or using other measures of exposure). Average median cumulative concentrations of $PM_{2.5}$ ranged from 14.3 to 15.9 µg/m³ for lag d 1 to the prior 60 d. No association was observed between PM_{10} and CRP or $PM_{2.5}$ and IL-6 (data not presented) (Diez-Roux et al., 2006).

Finally, in a single-city cross-sectional study significant associations between markers in nasal lavage and personal $PM_{2.5}$ (average: 30.4 ± 25.1 µg/m³) were observed in 41 Parisian asthmatic children (increases in eosinophils ($p < 0.05$), and exudation markers (urea ($p < 0.01$), albumin ($p < 0.01$) and alpha-1-antitrypsin ($p < 0.05$)). No significant results were reported in healthy children ($n = 44$; average personal $PM_{2.5}$: 42.4 ± 63.4 µg/m³) and no significant associations were observed with ambient PM_{10} in either group (average concentration for the 2 d before lavage: 21.9 ± 7.9 µg/m³ and 24.0 ± 8.2 µg/m³, in asthmatic and healthy children, respectively) (Nikasinovic et al., 2006).

14.5.5.4 Cardiovascular Effects

Mechanisms for the effects of air pollutants on cardiovascular endpoints have been proposed, including changes to the autonomic nervous system, changes in myocardial substrate such as injury, ischemia or hypertrophy, and changes in myocardial vulnerability predisposing individuals to arrhythmias or ischemia (Zareba et al., 2001). In the recent literature several endpoints have been studied, including heart rate and blood pressure, as well as HRV, heart rhythm, discharges from implanted cardioverter defibrillators (ICD) and dilation of the brachial artery.

In studies published since those assessed in the US EPA 2004 PM AQCD, arrhythmias have been measured using records of ICD discharges and ECG readings (measures of myocardial vulnerability) in a number of studies.

The use of discharges from ICDs, which detect arrhythmias, to investigate the effects of air pollution on cardiovascular functions has been studied both longitudinally and by case-

crossover analysis. No associations between pollutants and ICD discharges were observed in two related studies in Vancouver, BC. In the first study 4 years of ICD discharge data were collected from 50 subjects. Daily mean PM_{10} averaged $12.9 \pm 5.6 \mu\text{g}/\text{m}^3$. No associations were observed between PM_{10} and ICD discharges in the main analysis, in further analyses restricted to subjects who experienced 2+ or 3+ arrhythmias, or when data were stratified by season (numerical data not presented) (Vedal et al., 2004). In the companion report, which benefitted from more pollutant measurements (more monitors per pollutant and more pollutants), approximately 10 months of ICD discharge data were collected from 34 subjects. Average daily concentrations of $PM_{2.5}$, PM_{10} , EC and OC were $8.2 \pm 10.7 \mu\text{g}/\text{m}^3$, $13.3 \pm 4.9 \mu\text{g}/\text{m}^3$, $0.8 \pm 1.4 \mu\text{g}/\text{m}^3$ and $4.5 \pm 9.8 \mu\text{g}/\text{m}^3$, respectively. No significant associations with ICD discharges were observed (numerical data not presented); however, summertime estimates for EC and OC were positive, in contrast to negative estimates for the wintertime. This pattern was not observed for PM_{10} or $PM_{2.5}$ (Rich et al., 2004).

In a St. Louis, MO, study of 56 subjects followed for approximately 1.5 years, a positive but non-significant association between a $0.5 \mu\text{g}/\text{m}^3$ increase in EC and ventricular arrhythmia (OR = 1.18 (95% CI 0.93–1.50)) with a 24-h moving average was observed. Similar, but smaller associations were observed with 6-, 12- and 48-h moving averages. Associations with $PM_{2.5}$ (OR < 1) and OC (OR > 1) were not significant. Median 24-h mean concentrations of $PM_{2.5}$, EC and OC were 16.2, 0.6 and $4.0 \mu\text{g}/\text{m}^3$, respectively. The authors reported positive, non-significant findings for NO_2 , significant findings for SO_2 and no apparent increased risk with CO or ozone (Rich et al., 2006b).

In two analyses ($n = 203$, median 2-d mean concentration of $PM_{2.5}$ $10.3 \mu\text{g}/\text{m}^3$; and $n = 4$, median daily and hourly $PM_{2.5}$ concentrations 9.8 and $9.2 \mu\text{g}/\text{m}^3$, respectively) risk of ventricular arrhythmia measured by ICD discharge increased with increasing quintile of ambient $PM_{2.5}$ exposure in Boston. Subject follow-up was conducted between 1995 and 2002. Significant associations were only observed at higher quintiles, and stronger effects were observed when a prior arrhythmia had occurred within 3 d. In one study a $6.9 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ was associated with a RR of 1.60 (95% CI 1.30–1.96) when a previous arrhythmia had occurred within 3 d (Dockery et al., 2005), while in a second study the odds of this same event were 1.32 (95% CI 1.04–1.69) for a $7.8 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ (Rich et al., 2005). A similar effect of $0.74 \mu\text{g}/\text{m}^3$ BC was observed in the first study (RR = 1.74 (95% CI 1.28–2.37) while no association with BC was observed in the second. Gaseous pollutants (O_3 , CO and NO_2) were also associated with ventricular arrhythmias in both studies. In a subsequent analysis of the same data-positive, but non-significant associations with paroxysmal atrial fibrillation episodes were observed at lag 0 and lags 0–23 h (OR = 1.41 (95% CI 0.82–2.42) per $9.4 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ and OR = 1.13 (95% CI 0.63–2.03) per $7.8 \mu\text{g}/\text{m}^3$ $PM_{2.5}$, respectively). Associations with BC were weaker and also non-significant. The only pollutant associated with paroxysmal atrial fibrillation was lag 0 h ozone (Rich et al., 2006a).

Data on arrhythmias can also be collected from ECG readings. In one such study (6 monthly 24-h recordings per subject), it was reported that increases in supraventricular tachycardia were more strongly associated with elevated levels of UFPs, AMPs and $PM_{2.5}$ (24-h averages $12,602 \pm 6,455 \text{ n}/\text{cm}^3$, $1,593 \pm 1,034 \text{ n}/\text{cm}^3$ and $20.0 \pm 15.0 \mu\text{g}/\text{m}^3$, respectively) than changes in ventricular tachycardia in 57 older adult, male subjects with CHD residing in Erfurt, Germany. Significant increases (percentage change of GMs using linear regression) in ventricular tachycardia were associated with increases in all three pollutants 3 d prior to ECG readings (11.5% (95% CI 2.1–21.8%) per $10,005 \text{ n}/\text{cm}^3$ UFPs, 12.2% (95% CI 3.8–21.2%) per $1,299 \text{ n}/\text{cm}^3$ AMPs, and 6.9% (95% CI 1.8–12.3%) per $16.4 \mu\text{g}/\text{m}^3$ $PM_{2.5}$, respectively). By contrast, significant positive associations (RR using Poisson regression) between these pollutants and supraventricular tachycardia were reported at most lags, and were strongest for changes in

UFPs and PM_{2.5} 48–71 h prior to ECG readings (RR = 1.73 (95% CI 1.26–2.37) and RR = 1.31 (95% CI 1.08–1.58) per 10,005 n/cm³ and 16.4 µg/m³, respectively), and for changes in AMPs with a 5-d moving average (RR = 2.05 (95% CI 1.41, 2.97) per 1,299 n/cm³). Fewer effects were observed with the gaseous pollutants (NO, NO₂, CO and SO₂) (Berger et al., 2006).

Ectopy (extra heartbeats) may lead to arrhythmias. In subjects with COPD in Vancouver, BC, significant increases in natural logarithm-transformed supraventricular heartbeats (Ln-SVE) were significantly associated with estimated exposures to ambient and non-sulphate ambient PM_{2.5} (0.20 bph (95% CI 0.02–0.37 bph) per a 4.4 µg/m³ increment and 0.20 (95% CI 0.02–0.37 bph) per a 3.4 µg/m³ increment, respectively) and to ambient PM₁₀ (0.27 bph (95% CI 0.03–0.52 bph) per a 6.5 µg/m³ increment). A 5.8 µg/m³ increment of measured ambient PM_{2.5} was marginally associated with increased Ln-SVE (0.20 bph (95% CI 0.00–0.40 bph)). No significant associations were observed with measured ambient concentrations of PM₁₀, PM_{10–2.5} or ambient sulphate PM_{2.5}, estimated ambient concentrations of non-sulphate ambient PM_{2.5}, estimated exposure to ambient PM_{10–2.5}, measured exposure to ambient sulphate, measured personal exposure to PM_{2.5} or estimated exposure to non-ambient PM_{2.5} (Ebelt et al., 2005; study details presented in Section 14.5.5.2).

Ectopy was observed in two other studies. A 10 µg/m³ increment of 5-d moving average PM_{2.5} (24-h average: 19.6 ± 10.4 µg/m³) was significantly associated with supraventricular, but not ventricular, ectopy in subjects from Steubenville, OH, who participated in one or two 12-week sampling sessions. This effect was marginally significant in the main analysis, but became significant when heart rate was accounted for (OR = 1.48 (95% CI 1.02–21.5)). The association was stronger in subjects with hypertension (OR = 1.88 (95% CI 1.21– 2.92)) and those with more ectopic activity (supraventricular ectopy rates above the mean) (OR = 1.99 (95% CI 1.20– 3.29)), as well as subjects without bronchitis or asthma or those with a previous MI; however results for the latter groups were not significant. Stronger effects were observed with a 5-d average than daily average concentration of PM_{2.5}. Exposures to EC, NO₂, SO₂ and CO were not associated with effects, but significant effects were associated with SO₄²⁻ and O₃ (Sarnat et al., 2006c). In healthy male state troopers, PM_{2.5}Lightscatter was associated with increases in ventricular and supraventricular ectopic beats (19.1%, p = 0.045; and 23.0%, p = 0.014, respectively, per a 10 µg/m³ increment) (Riediker et al., 2004a; study details presented in Section 14.5.5.3).

Disturbances in cardiac rhythm may contribute to premature cardiovascular death (Spooner et al., 2001). An ECG measures changes in voltage over time (the depolarization/repolarization of the heart) that can be divided into distinct patterns of waves and intervals. Two types of studies have been used to investigate the effects of PM on changes to these patterns. One type characterizes the pattern of the waves, measuring myocardial substrate or vulnerability (amplitude, magnitude and slope of the waves). Changes in ST-segment depressions may be the result of MI, inflammation, a combination of these two, or ischemia. In the second type of study, changes in the time and frequency domains of HRV (the autonomic nervous system) are studied. It has been suggested that changes in HRV may be predictive of arrhythmias and increased risk of sudden cardiac death (Tsuji et al., 1996 and Stone and Godleski, 1999 *in* Elder and Oberdoster, 2006; Tapanainen et al., 2002 and Tsuji et al., 1996 *in* Park et al., 2006).

Different fractions of PM were associated with different measures of depolarization/repolarization of the heart. Significant ST-segment depressions were associated with BC, but not PM_{2.5} (median 5-h concentrations were 1.28 and 9.5 µg/m³, respectively) in one recent study of 28 Boston, MA, residents who were assessed once a week for 12 weeks. The strongest result was observed during rest after subjects had completed 5 min of exercise at lag 5 h (-0.11 mm (95% CI -0.18 mm to -0.05 mm) per 1.59 µg/m³ BC) and lag 12 h (-0.07 mm (95% CI -0.14

mm to -0.01 mm) per 0.89 $\mu\text{g}/\text{m}^3$ BC). By contrast, ST-segment depression was not associated with gaseous pollutants (Gold et al., 2005).

The ULTRA project was a multi-centre study inclusive of three concurrent panel studies conducted in Amsterdam, the Netherlands, Erfurt, Germany, and Helsinki, Finland, over a period of 6 months during the winter and spring of 1998/99. During this time older adults with CHD were followed up every 2 weeks. Certain endpoints were available for all three centres, while others were not and therefore are reported as single-city results.

In one study ($n = 5$) only data from Helsinki were evaluated because of too few ST-segment depression data in the other two locations. An increased risk of ST-segment depression >0.1 mV was associated with a 1,000 n/cm^3 increment of AMPs (OR = 3.29 (95% CI 1.57–6.92), a 10,000 n/cm^3 increment of $\text{NC}_{0.01-0.1}$ (OR = 3.14 (95% CI 1.56–6.32) and a 10 $\mu\text{g}/\text{m}^3$ increment of $\text{PM}_{2.5}$ (OR = 2.84 (95% CI 1.42–5.66) at lag 2 d. Median daily concentrations of $\text{NC}_{0.01-0.1}$, AMPs, PM_1 and $\text{PM}_{2.5}$ were 14,890 n/cm^3 , 1,200 n/cm^3 , 7.0 $\mu\text{g}/\text{m}^3$, and 10.6 $\mu\text{g}/\text{m}^3$, respectively. When data were stratified, lag 2 d associations with $\text{NC}_{0.01-0.1}$ were stronger when subjects with left bundle-branch block, left ventricular hypertrophy or anterolateral infarction were excluded, in women and in subjects without a history of MI. By contrast, lag 2 d associations with $\text{PM}_{2.5}$ were stronger when subjects with left bundle-branch block, left ventricular hypertrophy or anterolateral infarction were excluded, in men, in subjects with a history of MI and in subjects not taking beta-blockers. In two-pollutant models of different combinations of these fractions of PM, significant associations were generally observed, with the authors reporting independent associations for $\text{PM}_{2.5}$ and $\text{NC}_{0.01-0.1}$ when modelled together and suggestive evidence that results were most robust for PM_1 and $\text{NC}_{0.1-1}$. Significant increased risks of ST-depressions were also associated with NO_2 and CO (Pekkanen et al., 2002).

In a separate study conducted in Erfurt, PM-related changes in repolarization were observed in males with chronic heart disease ($n = 56$). There was no consistent lag structure across endpoints or pollutants, other than the observation that the strongest $\text{PM}_{2.5}$ -related effects were observed for lags 0–5 h prior to ECG for all endpoints. Increases in variability of T-wave complexity were similar for EC and OC (24-h averages: $2.6 \pm 2.4 \mu\text{g}/\text{m}^3$ and $1.5 \pm 0.6 \mu\text{g}/\text{m}^3$, respectively) with significant associations for both pollutants at lags 12–17 h and 0–23 h. The direction of percentage change in T-wave complexity was not always consistent, and effects were seldom positive and significant (only for UFPs at lag 18–23 h and $\text{PM}_{2.5}$ at 0–5 h). A 16.4 $\mu\text{g}/\text{m}^3$ change in $\text{PM}_{2.5}$ (24-h average: $20.0 \pm 15.0 \mu\text{g}/\text{m}^3$) was more strongly associated with T-wave amplitude depressions than changes of 1,299 n/cm^3 AMPs or 10,005 n/cm^3 UFPs (24-h averages $1,593 \pm 1,034 \text{n}/\text{cm}^3$ and $12,602 \pm 6,455 \text{n}/\text{cm}^3$, respectively) at lag 0–5 h ($-6.46 \mu\text{V}$ (95% CI $-10.88 \mu\text{V}$ to $-2.04 \mu\text{V}$); $-5.54 \mu\text{V}$ (95% CI $-9.51 \mu\text{V}$ to $-1.57 \mu\text{V}$); and $-5.91 \mu\text{V}$ (95% CI $-9.80 \mu\text{V}$ to $-2.01 \mu\text{V}$), respectively). A similar pattern of results was not observed at other lags. The strongest and most significant increases in Q-T corrected (QTc) interval were associated with a 0.7 $\mu\text{g}/\text{m}^3$ increase in OC (5.79 msec (95% CI 1.38–10.19 msec) at lag 0–23 h). These authors concurred with a previous study, suggesting that the differing effects observed with different fractions of PM may point to different mechanisms of action of PM on the repolarization process (Brook et al., 2004; Henneberger et al., 2005). Other studies of repolarization parameters are discussed in Section 14.5.7.

Other studies reported results across all three centres. Average mean daily concentrations of UFPs, AMPs and $\text{PM}_{2.5}$ ranged from 17,041 to 21,124 n/cm^3 , 1,390 to 2,131 n/cm^3 and 12.7 to 23.1 $\mu\text{g}/\text{m}^3$, respectively. Systolic and diastolic blood pressures (supine or standing) were decreased, most often significantly, in relation to increases of 10 $\mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$, 1,000 n/cm^3 AMPs and 10,000 n/cm^3 UFPs when data from all three centres were pooled. The strongest declines were observed with a 5-d average (-0.72 mm Hg (95% CI -1.92 – -0.49 mm Hg); -1.11 mm Hg (95% CI -2.12 mm Hg to -0.09 mm Hg); and -0.36 mm Hg (95% CI -0.99 – -0.27 mm Hg),

respectively, for supine systolic blood pressure. Declines in supine diastolic blood pressure were -0.70 mm Hg (95% CI -1.38 mm Hg to -0.02 mm Hg); -0.95 mm Hg (95% CI -1.53 mm Hg to -0.37 mm Hg); and -0.39 mm Hg (5% CI -0.75 mm Hg to -0.03 mm Hg), respectively). These effects were stronger in subjects with a previous MI than in those subjects without a MI. Declines in heart rate were only significantly related to AMPs at lag 2 d in Amsterdam, although marginal declines at the same lag were associated with AMPs and UFPs in all data pooled. Few effects were associated with CO or SO₂, and even fewer with NO₂ (Ibald-Mulli et al., 2004). The direction and significance of changes in HRV associated with 10 µg/m³ PM_{2.5} and 10,000 n/cm³ AMPs varied between cities, but in each city and in pooled results, significant effects of 10,000 n/cm³ UFPs were observed on the related endpoints Hfnu (HF/[HF+LF]) at lag 2 d and LF/HF at lags 1, 2 and 3 d and with a 5-d moving average. Pooled estimates at lag 2 d were 2.9% (95% CI 1.5–4.2%) and -13.5% (95% CI -20.1% to -7.0%), respectively. Declines in SDNN, HF and LF/HF were also associated with NO₂ and CO (Timonen et al., 2006).

Many studies have investigated the effects of air pollution on time and frequency domains of HRV. Some of these studies have identified other potentially susceptible groups. In a group of subjects with COPD in Vancouver, BC (study details presented in Section 14.5.5.2) declines in SDNN and RMSSD were non-significantly associated with measured concentrations and estimated exposures to ambient, non-ambient and fractions of PM. The only significant associations were for declines in RMSSD associated with the ambient concentration of PM₁₀ (-2.24 msec (95% CI -4.27 msec to -0.21 msec) per 7 µg/m³) and estimated exposure to non-sulphate ambient PM_{2.5} (95% CI -2.90 msec (95% CI -5.55 msec to -0.25 msec) per 4.2 µg/m³) (Ebelt et al., 2005).

In a study of 28 older adult residents of Boston, MA, examined once a week for up to 12 weeks, exposures to BC (24-h IQR 0.5 µg/m³; 1-h IQR 0.7 µg/m³) and PM_{2.5} (24-h IQR 13 µg/m³; 1-h IQR 10 µg/m³) were associated with declines in measures of HRV. A 1-h IQR of BC was associated with declines in SDNN (-4.6% (95% CI -2.0% to -7.2%)) and a 24-h IQR average with declines in SDNN, RMSSD and pNN50 (-5.1% (95% CI -1.5% to -8.6%), -10.1% (95% CI -2.4% to -17.2%) and -16.9% (95% CI -6.0% to -26.6%), respectively). While declines in HRV were associated with hourly PM_{2.5}, significance was only observed for associations between a 24-h increment of 10 µg/m³ and decreases of -10.1% (95% CI -2.8% to -16.9%) in RMSSD and of -12.7% (95% CI -1.6% to -22.5%) in pNN50. A stronger magnitude of effect was observed between 24-h average BC and SDNN in subjects with a previous MI (-12.7% (95% CI -5.7% to -19.25%) per 0.5 µg/m³ BC). Weaker associations were observed with gaseous pollutants. While associations with CO followed a similar pattern to that of BC, in a two-pollutant model only associations with BC remained significant (Schwartz et al., 2005a).

In a study in Atlanta, GA, the results observed for subjects with COPD (n = 18) and those who had experienced a recent MI (n = 12), who participated in one or two 7-consecutive-day sessions in fall or spring, were in opposite directions. Average 24-h concentrations of PM_{2.5} and EC were 17.8 and 2.3 µg/m³, respectively. One-h, 4-h and 24-h levels of PM_{2.5} were associated with non-significant declines in SDNN in subjects with a previous MI, but with significant increases in subjects with COPD (5.07% (95% CI 0.01–10.38%) and 8.29% (95% CI 1.71–15.30%) for increments of 10.66 and 11.65 µg/m³ of 1-h and 4-h PM_{2.5}, respectively). Non-significant declines in other HRV parameters were associated with PM_{2.5}, but the only other significant association was with increases in LF in subjects with COPD (35.88% (95% CI 6.79–72.90%) per 11.65 µg/m³ of 4-h PM_{2.5}). Effect modification by medication use also had opposite effects in these groups, with declines in SDNN associated with 4-h PM_{2.5} in subjects using beta-blockers (primarily those with COPD; -7.3% (95% CI -13.8% to -0.35%) and increases in SDNN associated with 4-h PM_{2.5} in subjects taking sympathomimetics (primarily those with a previous MI; data not reported). No effect modification was observed with medications taken by both

groups of subjects (data not reported). In all subjects pooled, baseline FEV₁ modified the association between pollutants. A 10.6 µg/m³ increment of 4-h PM_{2.5} was associated with a non-significant decline in SDNN in subjects in the 90th percentile of FEV₁, but a significant increase in SDNN was observed among those in the 10th percentile (10.2% (95% CI 3.8–17.0%)). By contrast, a 1.7 µg/m³ increment in 4-h EC was associated with a decline in SDNN among subjects in the 90th percentile of FEV₁ (-3.95% (95% CI -7.4% to -0.3%)), but a non-significant increase in SDNN in the 10th percentile. Strong associations were observed with NO₂, but not other gases or EC (Wheeler et al., 2006).

In a second study that considered effect modification by medication status in 32 older adults in Steubenville, OH, observed weekly during summer and fall, stronger effects were observed in “healthier” subjects (i.e., those without hypertension or those not taking medication). In all subjects combined a 13.4 µg/m³ increment of PM_{2.5} at lag d 1 was associated with significant declines in RMSSD, SDNN, HF and LF. Similar results were reported at shorter lags (4–72 h). In subjects with hypertension the association with RMSSD was -2.0% (95% CI -8.5–4.8%) and in subjects without hypertension, -17.8% (95% CI -25.8% to -8.9%). The p-value for interaction was 0.002. No effect modification was observed with coronary artery disease or CHF. No significant declines in RMSSD were associated with PM_{2.5} in subjects taking beta-blockers or statins, but in those not taking these medications, significant declines were observed (-10.0% (95% CI -16.0% to -3.4%) and -8.4 (95% CI -14.4% to -2.0%), respectively). For these two groups, p-values for interaction were 0.03 and 0.15, respectively. The mean 24-h average PM_{2.5} concentration was 19.7 µg/m³. Associations with SO₄²⁻, but not EC, NO₂, SO₂ or O₃ were also observed. The authors speculated that the small sample size may have made it difficult to see true effects, or that detecting an air pollution effect among other influences (e.g. medication use) may be difficult (Luttmann-Gibson et al., 2006).

In a study of 19 older adult subjects with CHD from two centres in the Coachella Valley, CA, who participated in up to 12 weekly 24-h ECG monitoring sessions, significant declines in SDNN, TRII (triangular index) and total power were associated with ambient PM₁₀ and PM_{10-2.5}, while non-significant declines were associated with exposure to PM_{2.5}. Significant associations were observed with 2-, 4-, 6- and 8-h, but not 24-h moving averages. The greatest declines in PM₁₀-associated changes in SDNN and SDANN were with a 6-h moving average (-1.45% (SE 0.54%), p = 0.008; and -1.80% (SE 0.738%), p = 0.016, per a 10 µg/m³ increment), and the strongest decline in TRII was observed with an 8-h moving average (-1.46% (SE 0.563%), p = 0.011). Daily concentrations of PM₁₀ and PM_{2.5} averaged 46.1 and 23.2 µg/m³ in one location, and 31.0 and 14 µg/m³ in a second location (Lipsett et al., 2006).

Most significant declines in HRV have been observed in older adults, often with a pre-existing disease. However, effects have also been observed in healthy subjects and no effects were observed in one study. In older, healthy adult residents of Utah declines in SDNN and RMSSD were associated with PM_{2.5} at lag d 0 (35 msec (SE 8 msec), p < 0.01 and 42 msec (SE 11 msec), p < 0.01 per a 100 µg/m³ increment) (Pope et al., 2004a; study details presented in Section 14.5.5.3). In North Carolina state troopers, effects were in the opposite direction to the majority of results from studies of potentially susceptible populations. Significant increases in mean cycle length of R-R intervals for normal beats (MCL) (4.2%, p < 0.003), SDNN (11.7%, p < 0.006), pNN50 (12.2%, p < 0.009), HF (14.8%, p < 0.019) and LF/HF (-21.5%, p < 0.007) were associated with in-vehicle PM_{2.5}Lightscatter the morning after a 3 p.m. to midnight shift. Only MCL was statistically associated with PM_{2.5} mass (6.3%, p < 0.005). Central site urban ambient concentrations of PM_{2.5} (average: 32.3 µg/m³) were not significantly associated with any endpoints (data not presented) (Riediker et al., 2004a; study details presented in Section 14.5.5.3). In one study of 34 older adults with or without CVD in Seattle, WA, followed for one to

three 10-d sessions, no associations were observed between fairly low levels of PM_{2.5} (1-h mean 10.7 µg/m³) and HF, RMSSD or SDNN (Sullivan et al., 2005b).

Both increases and decreases in heart rate have been observed in relation to PM. In subjects with COPD from Vancouver non-significant increases in heart rate were associated with ambient concentrations of, and estimated exposures to, ambient PM₁₀, PM_{10-2.5}, PM_{2.5} and non-sulphate PM_{2.5}. Non-significant declines were associated with estimated exposure to non-ambient PM_{2.5}, total personal PM_{2.5}, exposure to ambient sulphate PM_{2.5} and ambient concentration of sulphate PM_{2.5} (Ebelt et al., 2005). In older adults with CHD from three European cities, marginally significant declines in heart rate were associated with UFPs, AMPs and PM_{2.5} at lag 2 d. The only significant declines were observed with AMPs in Amsterdam (data presented graphically) (Ibald-Mulli et al., 2004). In healthy subjects and those with respiratory or heart disease, pooled, a 10 µg/m³ increment in personal PM_{2.5} was associated with a significant increase in heart rate (0.44 bpm (95% CI 0.04–0.84 bpm) and a 10 µg/m³ increment in local outdoor PM_{2.5} was associated with a significant decline in heart rate (-0.75 bpm (95% CI -1.42 bpm to -0.07 bpm) at lag d 0. When stratified by underlying disease and medication use, consistent significant declines in heart rate were only observed in healthy subjects not taking medication (Mar et al., 2005a; study details presented in Section 14.5.3.2). In a Steubenville study a 13.4 µg/m³ increment of PM_{2.5} at lag d 1 was associated with significant increases in heart rate (1.1% (95% CI 0.2–2.1%)) with similar, but non-significant results reported for SO₄²⁻, non-sulphate PM_{2.5}, NO₂, SO₂ and O₃ (Luttman-Gibson et al., 2006; study details presented earlier).

Changes in blood pressure were often observed, primarily in older subjects, but the direction of change was mixed, although the magnitudes of the declines in blood pressure were smaller than any observed increases. In a Vancouver study of subjects with COPD, Ebelt et al. (2005; study details presented in Section 14.5.5.2) observed non-significant declines in systolic blood pressure associated with ambient exposures and non-ambient exposures to PM₁₀, PM_{2.5} and PM_{10-2.5}. Significant associations were only observed, however, with estimated ambient concentrations of non-sulphate PM_{2.5} (-1.52 mm Hg (95% CI -2.94 mm Hg to -0.09 mm Hg) per 4.2 µg/m³), estimated exposure to non-sulphate ambient PM_{2.5} (-1.70 mm Hg (95% CI -3.27 mm Hg to -0.14 mm Hg) per 3.4 µg/m³) and estimated exposure to ambient PM_{2.5} (-1.90 mm Hg (95% CI -3.66 mm Hg to -0.14 mm Hg) per 4.4 µg/m³), even though, on average, non-ambient exposures comprised the majority of subjects' exposure to total PM. Non-significant declines in diastolic blood pressure were associated with ambient concentrations and estimated exposures to PM₁₀, PM_{10-2.5}, PM_{2.5} and non-sulphate PM_{2.5}, while non-significant increases were associated with exposure to ambient sulphate, total personal exposure to PM_{2.5} and estimated exposure to non-ambient PM_{2.5}. In older adults with CHD in three European centres declines in blood pressure in a supine position were similar, but often more significant, than measurements taken in a standing position. In pooled analyses, 5-d averages of UFPs, AMPs and PM_{2.5} were significantly associated with diastolic blood pressure in a supine position (-0.70 mm Hg (95% CI -1.38 mm Hg to -0.02 mm Hg) per 10,000 n/cm³ UFPs, -0.95 mm Hg (95% CI -1.53 mm Hg to -0.37 mm Hg) per 1,000 n/cm³ AMPs, and -0.39 mm Hg (95% CI -0.75 mm Hg to -0.03 mm Hg) per 10 µg/m³ PM_{2.5}). Five-day average AMP was also associated with a significant decline in systolic blood pressure (-1.11 mm Hg (95% CI -2.12–0.09 mm Hg)) (Ibald-Mulli et al., 2004; study details presented earlier). Few significant increases in systolic or diastolic blood pressure were observed in Seattle in healthy subjects, subjects with respiratory disease and subjects with heart disease in pooled analyses, or in analyses stratified by underlying disease and medication use when subjects were followed for one or more 10-d sessions over 3 years. In subjects with heart disease taking any medication, a 10 µg/m³ increment of personal PM_{2.5} was associated with a significant increase in systolic blood pressure at lag d 0 (4.2 mm Hg (95% CI 1.04–7.37 mm Hg)). The authors also reported increases in systolic blood pressure in relation to indoor

PM_{2.5} and local outdoor PM₁₀ (numerical data not presented) (Mar et al., 2005a; study details presented in Section 14.5.5.2). Finally, in older adults with CVD (data collected over 3 years) a 10.4 µg/m³ increment of 120-h average PM_{2.5} was associated with the greatest increases in resting diastolic (2.82 mm Hg (95% CI 1.26–4.41 mm Hg), systolic (2.68 mm Hg (95% CI 0.04–5.38 mm Hg) and mean arterial (2.76 mm Hg (95% CI 1.07–4.48 mm Hg) blood pressure. When subjects were stratified by heart rate, 48-, 96- and 120-h average PM_{2.5} levels were associated with diastolic blood pressure during exercise in subjects with heart rate ± 70 bpm (6.95 mm Hg (95% CI 2.11–12.11 mm Hg) per 13.9 µg/m³, 5.46 mm Hg (95% CI 1.69 – 9.43 mm Hg) per 10.7 µg/m³, and 4.72 mm Hg (95% CI 0.92 – 8.72 mm Hg) per 1.04 µg/m³, respectively). In this same group of stratified subjects, 48-h and 96-h PM_{2.5} levels were associated with mean arterial blood pressure (4.32 mm Hg (95% CI 0.04–8.79 mm Hg) and 3.56 mm Hg (95% CI 0.20–7.04 mm Hg), respectively) (Zanobetti et al., 2004).

The effects of PM on cardiovascular endpoints were also observed in acute cross-sectional studies. These studies, which included only one measurement per subject, are presented here for ease of comparison with respect to endpoint, not study design. Subjects from the US ARIC Study with hypertension had greater increases in heart rate and decreases in HF and SDNN associated with an 11.5 µg/m³ change in PM₁₀ at lag d 1 than all subjects pooled. In all subjects these changes were 0.32 bpm (p < 0.01), -0.06 ms² (p < 0.01) and -1.03 msec (p < 0.01), respectively, compared with changes in hypertensive subjects of 0.69 bpm (p < 0.01), -0.08 ms² (p < 0.01) and -1.29 msec (p < 0.01), respectively. The average daily PM₁₀ concentration was 24.3 ± 11.5 µg/m³. Similar, but generally weaker results were observed with the gaseous pollutants O₃, SO₂, CO and NO₂ (Liao D et al., 2004). In a cohort of 497 older adult male subjects from the VA Normative Aging Study (2000–03) in Boston, MA, Park SK et al. (2005) observed non-significant associations between BC (24-h moving average: 0.92 ± 0.47 µg/m³) and PN (24-h moving average: 28,942 ± 13,527 n/cm³) and HRV. Significant changes in HRV were associated with an 8 µg/m³ increase in the 48-h moving average of PM_{2.5} (24-h moving average: 11.4 ± 8.0 µg/m³). In all subjects, declines in log₁₀HF were -20.8% (95% CI -34.2% to -4.6%) and increases in log₁₀LF/HF were 18.6% (95% CI 4.1–35.2%). Similar, but non-significant declines in SDNN and LF were observed, and results from two-pollutant models with ozone were similar. When subjects were stratified by underlying disease, effects associated with PM_{2.5} (HF, LF/HF) were significant in subjects with hypertension (n = 335), and of greater magnitude than in those without hypertension (SDNN, HF, LF, LF/HF; groups not compared statistically). However, significant effects were also observed in subjects using beta-blockers (n = 163; LF/HF), with greater effects on SDNN, HF and LF/HF observed compared with those not using beta-blockers. Changes in all HRV parameters measured were greater in subjects not using calcium channel blockers (n = 427) or ACE inhibitors (n = 397) than in those using these medications. Stronger, but non-significant declines in some measures of HRV were reported in subjects with IHD (n = 142) than in subjects without IHD, and in subjects with diabetes (n = 72) compared with subjects without diabetes. Effects were also associated with ozone, but not other gaseous pollutants (NO₂, CO, SO₂).

In two other studies of participants of the Normative Aging Study, gene–environment interactions were studied (see Section 14.7 for further details). The effects of PM_{2.5} (48-h average 11.4 ± 8.0 µg/m³) on HRV measurements (HF) were greater in subjects who were genotyped GSTM1 *null* (-34% (95% CI -9% to -52%) vs. -27% (95% CI -8% to -42%) in all subjects) for a 10 µg/m³ increase in 48-h average PM_{2.5}. No significant association was observed in subjects genotyped GSTM1 *wt*. Within the group of subjects genotyped GSTM1 *null* declines in HRV were only significant for subjects not taking statins (-34% (95% CI -53.0% to -7.20%)). There was a trend towards greater decreases in HF in obese subjects or subjects with high neutrophil counts who were genotyped GSTM1 *null* rather than GSTM1 *wt*. (Schwartz et al., 2005b). In the second study, subjects were stratified by HFE (the hemochromatosis gene,

which has a role in modulating Fe uptake) variants, and associations between PM_{2.5} (48-h moving average: 11.7 ± 7.8 µg/m³) and HRV were only observed in subjects with the wild-type HFE gene (-31.7% (95% CI -48.1% to -10.3%) in HF per 10 µg/m³ 48-h moving average PM_{2.5}; changes in other variables were reported to be similar but data were not presented (Park et al., 2006).

Vascular reactivity and endothelial function were studied using pooled baseline data of flow-mediated and nitroglycerin-mediated reactivity (measures of changes in brachial artery diameter) from four Boston, MA, clinical studies of diabetic subjects or subjects at risk for diabetes (n = 100). Declines in flow-mediated reactivity were associated with a 6-d moving average of BC (24-h average: 1.0 ± 0.6 µg/m³) in subjects with diabetes (-21.7% (95% CI -21.7% to -2.4%) per IQR (not reported)). Similarly, declines in nitroglycerin-mediated reactivity were associated with 6-d moving averages of PM_{2.5} (24-h average: 11.5 ± 6.4 µg/m³) in subjects with diabetes and all subjects pooled (-7.6% (95% CI -12.8% to -2.1%) and -6.2% (95% CI -11.0% to -1.1%), per IQR (not reported), respectively). A 6-d moving average of PN (24-h average: 36,155 ± 12,490 n/cm³) was also associated with non-significant decreases in nitroglycerin-mediated and flow-mediated reactivity in diabetics. All the changes in subjects with diabetes were driven by Type II diabetics; no significant associations were observed in subjects with Type I diabetes. Associations with air pollutants were stronger when hormone replacement therapy, birth control or alcohol use was controlled for (data not presented). The authors attributed a lack of UFP-associated effects associated to a greater potential for exposure misclassification with this fraction of PM. Overall, the greatest effects were associated with SO₄²⁻, not PM (O'Neill et al., 2005).

In other cross-sectional studies decreases in systolic blood pressure were associated with PM₁₀ (average daily concentration: 20.36 ± 9.97 µg/m³) in 2612 older adult French subjects (-1.12 mm Hg (95% CI -1.90 mm Hg to -0.30 mm Hg) per 10 µg/m³ PM₁₀ at lag 5 h) (Harrabi et al., 2006), but not associated with lag 0 or 1 d PM₁₀ or PM_{2.5} (average mean ambient concentrations the day before examination: 22.0 ± 10.6 and 12.6 ± 5.0 µg/m³, respectively) in 16,756 adult Norwegians (data not reported) (Madsen et al., 2006).

Many other studies have been conducted in other environments, which are considered poor surrogates for Canadian exposures, often because of very high ambient concentrations of pollutants. Therefore these studies conducted outside Canada, the US and Europe, in Asia and Central and South America are judged to be less relevant. Positive associations were observed in the majority of studies (Holguin et al., 2003; Volpino et al., 2004; Chan et al., 2004, 2005; Chuang et al., 2005a, 2005b; de Paula Santos et al., 2005; Riojas-Rodriguez et al., 2006; Vallejo et al., 2006). The results from a double-blind random design study of nursing home residents in Mexico City suggested that fish-derived omega 3 fatty acids reduced the effects of PM_{2.5} on HRV. This evidence for a protective effect of antioxidants contributes to a growing literature on the role of oxidative damage in particulate-related adverse effects (Romieu et al., 2005).

14.5.5.5 Summary and Considerations: Panel Studies

In general, results from recent panel studies (identified after the cut-off date for the US EPA 2004 PM AQCD) are in line with the conclusions of previous assessments and have advanced our knowledge of the associations between PM and respiratory and cardiovascular endpoints. In recent years associations between PM_{2.5} and cardiac endpoints have been investigated in panel studies more than any other outcome, providing evidence across a range of endpoints that exposure to PM results in changes in cardiovascular parameters. At the same time, evidence is growing to support associations between PM and more subtle cellular and biochemical

endpoints, and research continues to identify a range of severity of adverse respiratory outcomes associated with exposure to PM.

Recent Canadian panel studies were limited to three investigations in Vancouver, BC. In one study of subjects with COPD, estimated exposures to PM₁₀, PM_{10-2.5}, PM_{2.5}, non-sulphate PM_{2.5} and sulphate PM_{2.5} were more associated with declines in lung function and blood pressure, increases in supraventricular heartbeats and mixed changes in heart rate and HRV than were ambient concentrations of these pollutants. In two companion articles no associations between PM and ICD discharges were observed. While one study benefitted from more pollutant data, it was observed that null effects in these studies may have been influenced by low power ($n \leq 50$), dilution of effects (pooled arrhythmia data) or over-controlling for confounding factors.

Evidence from new studies of respiratory endpoints is generally consistent with the conclusions of the 1999 PM SAD and the US EPA 2004 PM AQCD. Similarly to the findings of these two assessments, declines in lung function and increases in respiratory symptoms were observed in studies of asthmatic subjects in the recent literature. The majority of these studies were conducted in children, and in the one study that compared children and adult asthmatics, significant effects were only observed in the former group. In several of these more recent studies in asthmatic children, personal PM_{2.5} was associated with declines in lung function, and these associations were sometimes of greater strength than those with ambient concentrations of PM_{2.5}; in some studies of only ambient concentrations no associations between PM and lung function were observed. The more recent literature has also provided some evidence for increased susceptibility to declines in lung function or increased respiratory symptoms in asthmatic subjects taking medication compared with those not taking medication (three of four studies). Associations between PM and increased medication use were also observed, but not across all studies.

The results of several recent studies also suggest that in addition to asthmatics, subjects with COPD may be at greater risk for decrements in lung function associated with PM. There was little evidence for increased use of medication or respiratory symptoms in these subjects. As in the US EPA 2004 PM AQCD, declines in lung function and increases in respiratory symptoms associated with PM were also observed in healthy subjects. Significant findings in healthy subjects were generally limited to studies of children; few significant effects were observed in studies of adults.

Across studies that investigated measures of respiratory health, the most studied fractions were PM₁₀ and PM_{2.5}. In healthy subjects results for BS were often similar to associations with PM₁₀ and in asthmatic subjects no consistent pattern of relative magnitude of effect was observed for associations with PM_{2.5} and PM₁₀. Stronger effects were associated with gaseous pollutants in some studies. Lags of 0 to 7 d as well as moving averages up to 5 d were included in these studies. It was noted that declines in lung function associated with PM₁₀ varied temporally, but too little data were available to assess the effects of seasonality.

Following the 1999 PM SAD in which no studies of biomarkers were identified, and the US EPA 2004 PM AQCD in which alterations in some haematological parameters (e.g. CRP, fibrinogen, blood viscosity) were associated with PM, the more recent literature has provided further evidence for associations between PM and alterations in levels of biomarkers, especially markers of inflammation. Changes in biomarkers were observed across all fractions examined (PM_{2.5}, PM₁₀, UFPs, OC, EC and AMPs), with PM_{2.5} being the most widely studied fraction using short lag structures, including hourly lags. Similarly to studies of respiratory endpoints, asthmatic children were the most investigated group of subjects. Results suggested a fairly consistent association between FeNO and exposure of asthmatic subjects to air pollution. PM-related increases in FeNO in asthmatic children occurred earlier and were stronger than those

observed in older adults, including subjects with COPD, asthma, or, asthma and COPD; however, this observation is based on a limited number of studies ($n = 5$). As in the findings of the US EPA 2004 PM AQCD, significant increases in CRP were associated with PM, including in studies of young healthy males, healthy older subjects and older subjects with diabetes, obesity or hypertension. Changes in biomarkers associated with pathways leading to coronary events have been reported in subjects with CHD (e.g. increases in CRP (inflammation), FVII and prothrombins (coagulation cascade) and vWF (platelet adhesion)). Evidence for associations between other specific biomarkers and PM was less strong, in part because they have been studied less. The results from cross-sectional studies for similar acute outcomes supported the findings of panel studies.

While no studies of cardiovascular endpoints were identified at the time of the 1999 PM SAD, the US EPA 2004 PM AQCD observed that PM was associated with declines in markers of cardiac function (e.g. HRV) in panels of older adults. It was concluded that these results provided only very limited suggestive evidence of pathophysiologic alterations that contribute to serious PM-related cardiovascular effects (MI, stroke, mortality); however, the breadth of changes was suggestive of a chain of endpoints linked to potential mechanisms of action for cardiovascular-related effects. In the recent literature, significant findings, not necessarily consistent across endpoints, were reported in almost all the studies of cardiovascular endpoints (heart rate, blood pressure, HRV, ectopy and arrhythmias) that were reviewed. There is evidence from recent studies that PM has effects on measures of key factors of cardiac death, especially autonomic nervous system control and myocardial vulnerability, and to a lesser extent myocardial substrate. While changes in heart rate and blood pressure varied by study, PM was positively associated with ectopy. Ectopy may lead to arrhythmias, which were also significantly associated with PM, in addition to changes in repolarization of the heart and HRV. Results from a cross-sectional study indicated that PM was associated with reduced vascular reactivity (declines in dilation of the brachial artery). The only subpopulation to be consistently associated with increased susceptibility was subjects with hypertension, who were identified as more susceptible to the effects of PM on ectopy and HRV in panel studies, as well as HRV and heart rate in cross-sectional studies. A range of lags were examined in these studies, but no conclusive indication can be ascertained of which lag period(s) demonstrate the strongest associations.

Across studies that investigated cardiovascular endpoints, the fine fraction of $PM_{2.5}$ was examined most frequently, followed by BC/EC/OC and PM_{10} . The number of studies that involved an examination of particle fractions smaller than 2.5 microns can be attributed to the findings from the ULTRA study. Both hourly and daily lags and moving averages were studied, and there was little evidence of trends in effects based on lag structure, although there were few studies of delayed lags. It was proposed that smaller particles may have more of an effect than larger fractions and there was some support for this statement, given a lack of significant associations with PM_{10} and $PM_{10-2.5}$ in several studies. There were too few data to compare the relative effects of UFPs and $PM_{2.5}$. The magnitudes of effects associated with particulate and gaseous pollutants were mixed. Except for one study, subjects were older and most had a pre-existing disease.

Alterations in respiratory and cardiovascular parameters, as well as biomarkers, have been observed across all fractions of PM. It is difficult to draw conclusions on the importance of different size fractions, especially as different results were observed across studies of different endpoints that examined multiple fractions. When PM_{10} or $PM_{10-2.5}$ was measured, their associated effects were often weaker than other fractions. Across endpoints, measures of personal exposure were more strongly associated with effects than local ambient or central

monitors in several studies, whereas in other studies associations with concentrations at central sites, outdoors or indoors were clearer.

In two small panel studies, the ambient and non-ambient components of personal exposure were estimated separately for each participant. In a study of 16 COPD patients, Ebel et al. (2005) found that ambient exposures (and to a lesser extent ambient concentrations) were associated with decreased lung function, decreased systolic blood pressure, increased heart rate and increased SVE heartbeats, whereas total and non-ambient particle exposures were not associated with any of the health outcomes. In this study, the ambient exposure to PM_{2.5} was more strongly related to the ambient concentration ($R^2 = 0.62$) than total exposure ($R^2 = 0.07$) and non-ambient exposure was not related ($R^2 < 10^{-6}$) (Wilson and Brauer 2006). Similarly, in a study of 16 asthmatic children, Koenig et al. (2005) reported that the ambient component of exposure, but not the non-ambient component, was significantly associated with an increase in exhaled NO in participants who were not using corticosteroid therapy. These studies provide support for the use of ambient concentrations of PM as a surrogate for ambient exposure, demonstrate the usefulness of separating total personal exposures into their ambient and non-ambient components, and confirm that non-ambient exposures will not confound the association between ambient PM and health effects.

Traffic-related pollutants have been implicated in the adverse effects observed in several studies. In some studies, traffic-related pollutants (e.g. NO₂ or BC), were more robustly associated with adverse effects than PM. Too few data are available to draw conclusions on the possible roles of components of PM in eliciting health effects, though there is some evidence implicating transitional metals in the recent literature; it was reported that differences in the ability to take up Fe (measured by variations in HFE) altered the effects of PM on HRV, and that Zn, Cr, Fe and Ni components of PM_{2.5} were associated with declines in lung function.

14.5.6 Intervention Studies

Intervention studies (often involving features of time-series design) investigate natural or man-made changes in the environment that result in changes in airborne pollutant concentrations. Air health effects researchers analyze differences in specific health endpoints before and after a given intervention. This type of study provides a powerful tool for identifying a possible causal relationship between air pollutants and human health effects. If possible, these studies should imply situations where socioeconomic conditions remain the same in order to avoid changes that may confound or mask an effect of air pollution reduction.

14.5.6.1 Summary of Previous Assessments

Only one intervention study was reviewed in the 1999 PM SAD. Pope (1989) studied the impacts of the closure and subsequent re-opening of a steel mill on air quality and hospital admissions for respiratory diseases among children. Analyses of children's respiratory admissions before and after the steel mill closure made evident a decreased morbidity resulting from the lower PM₁₀ concentrations during the mill closure.

Following the publication of the 1999 PM SAD two intervention studies were reviewed in the US EPA 2004 PM AQCD. In both studies regulations caused a sudden reduction in PM and/or SO₂ and sulphate. A ban on the sale of coal in Dublin, Ireland (Clancy et al., 2002) was associated with major declines in BS and significant reductions in mortality, especially for cardiovascular and respiratory disease causes, suggesting that control of particulate air pollution can lead to immediate and significant reductions in death rates. The second study (Hedley et al., 2002) assessed the impacts of a regulatory action in Hong Kong to limit the sulphur content of fuel oil. Declines in mortality were observed in the year following the intervention, a period when there

were reductions in SO₂ and to a lesser extent, respirable sulphate particles, though there was no reduction in PM₁₀.

14.5.6.2 Intervention Studies

In the current review, six intervention studies have been identified. Most of these have been carried out in Europe; none in Canada. The studies reviewed include some situations in which the intervention was abrupt and others where the intervention occurred more gradually, as well as studies in which the health outcomes were related to either short-term or chronic exposure to PM.

An important study on air pollution reduction was carried out by Laden et al. (2006), who reanalyzed the Harvard Six Cities study (Dockery et al., 1993) using data from 1979 to 1998. This cohort study with a focus on all-cause and cardiovascular mortality has been described in the chronic mortality section (14.8.1.2). Decreases in annual mean PM_{2.5} concentrations were observed across all cities during the study period; a diminution in overall mortality was also noted. A reduction of 10 µg/m³ in PM_{2.5} was associated with a significant reduction (-27% (95% CI -43% to -5%)) in total mortality when comparing average PM_{2.5} levels between 1990 and 1998 to 1980–1985 levels. An increase of 10 µg/m³ in the average annual PM_{2.5} was also associated with an increase in all-cause mortality of 17% (95% CI 8.0–26%) and 13% (95% CI 1.0–27%) for the 1974–1989 and 1990–1998 periods, respectively. For the entire period (1974–1998), an increase of 16% (95% CI 7–26%) was reported; it declined to 14% (95% CI 6.0–22%) when annual PM_{2.5} average (concentration in the year of death) was considered. Cardiovascular mortality was also positively associated with PM_{2.5} over the entire study period (28% (95% CI 13–44%)) while a non-significant association was observed for respiratory mortality (8% (95% CI -21–49%)) and lung cancer (27% (95% CI -4–69%)). A reduction of 10 µg/m³ in PM_{2.5} was associated with a non-significant reduction in cardiovascular mortality (-31% (95% CI -54–10%)) and in respiratory mortality (-57% (95% CI -84–13%)) when comparing average PM_{2.5} levels for the periods 1990–1998 and 1980–1985.

In Switzerland, a cross-sectional survey was conducted to study respiratory diseases in schoolchildren from 1992 to 2001 (Bayer-Oglesby et al., 2005). This study was carried out to assess the health effects associated with the implementation of air pollution abatement measures. Children in nine centres that had varied levels of air pollution, urbanization and climatic conditions were observed at two time points 6 to 8 years apart. Questionnaires including core questions from the International Study of Asthma and Allergy in Childhood (ISAAC) were completed by parents. Multi-logistic regression models were used to analyze the changes in nine respiratory health endpoints associated with variations in air pollution. PM₁₀ decrease adjusted ORs were controlled for potential confounders, including socioeconomics (age, sex, nationality, parental education, number of siblings, farming status), health factors (low birth weight (LBW), breastfeeding, child who smokes, family history of asthma and/or bronchitis), indoor factors (mother who smokes, humidity, mode of heating and cooking, carpeting, pets allowed in bedroom), questionnaire-related factors and avoidance behaviour with respect to allergies. A dummy variable for the month was also included in the model to adjust for possible reporting bias.

An overall average decline of 9.8 µg/m³ was observed for PM₁₀ from 1993 to 2000; a 3-fold higher reduction was reported in urban and suburban areas. In healthy children an association between decreasing levels of PM₁₀ (as a result of air pollution abatement measures) and reduced respiratory symptoms was observed. The prevalence of non-allergy-related and allergy-related symptoms decreased over time as PM₁₀ levels declined; however, only decreases in non-allergy related symptoms (e.g. chronic cough (-34.4% change), bronchitis (-39.9% change), common cold (-25.4% change), nocturnal dry cough (-29.0% change) and

conjunctivitis (-23% change)) were significant. Conversely, prevalence of asthma (-8.7% change) and hay fever (-4.6% change) also declined, but this was not statistically significant. The strongest declines in health effects were observed in urban and suburban areas, where PM₁₀ levels dropped the most (approximately 12.7%), compared with rural and alpine areas, where declines in PM₁₀ were more modest (approximately 4%). Across all regions, the mean change in annual average PM₁₀ was associated with the mean change in adjusted prevalence of nocturnal dry cough, chronic cough and conjunctivitis. No threshold for effects was observed in this study.

Epidemiologic findings have suggested that respiratory illness or reduced lung function are associated with proximity to main streets/roads, with road density, or with exposure to pollution derived from motor vehicles. A road bypass to ease traffic congestion in one neighbourhood was built in an industrial town in North Wales, UK. A substantial reduction in the volume of “heavy goods” traffic was observed following the construction of this road bypass, as well as a reduction in PM air pollution. Burr et al. (2004) investigated whether residents of the congested area had a higher prevalence of respiratory symptoms and whether their respiratory health improved following a reduction in exposure to traffic-related air pollution as compared with residents of a nearby uncongested area. PM₁₀ and PM_{2.5} levels were higher at baseline in the congested area than in the less congested area. After the bypass opened, PM₁₀ ambient concentrations decreased by 23% (from 35.2 µg/m³ in 1996–1997 to 27.2 µg/m³ in 1998–1999) in the congested streets area and by 29% (from 11.6 µg/m³ in 1996–1997 to 8.2 µg/m³ in 1998–1999) in the less congested streets area. PM_{2.5} levels, which were roughly two-thirds those of PM₁₀, declined by similar percentages as PM₁₀. A comparison was performed by surveying 165 residents of the congested streets and 283 residents of the low-traffic streets 1 year before and after the construction of the road bypass. PEFr measurements were carried out and repeated after the opening of the road bypass at the same times of the year and using the same methodology, to allow comparison of the situation before and after the by-pass opening. No clear or consistent differences were initially found between the residents of the two areas in terms of respiratory symptoms or peak flow variability. The only statistically significant difference observed ($p < 0.05$) was related to rhinitis that interfered with daily activities, the prevalence being higher for the congested area (7.6% in the congested area vs. 4.1% in the less congested area). After the repeated questionnaire and PEFr measurements were carried out, the “net % better” was expressed as the number of persons who improved minus the number of persons who deteriorated and was expressed as a percentage of the total available. A trend of improvement in symptoms was observed in both areas after the opening of the bypass. Wheeze in the congested area showed a lower, but not significant, net improvement compared with the less congested streets (a 6.5% net reduction (95% CI -14.9–2.0%)), and a marked improvement was also observed for subjects who consulted a doctor for chest trouble (net 5.7% better in the congested area and a net 4.5% better in the less congested area, for a net 1.3% reduction (95% CI -8.1–10.7%)). Rhinitis was improved in both areas, but the change was greater in the congested area, with a 10.3% difference for rhinitis interfering with daily activities (95% CI 3.1–7.5%), and positive but non-significant differences for any rhinitis or for rhinoconjunctivitis. This new study has suggested that decreased PM exposure as a result of traffic reduction may offer more relief from nasal and eye symptoms than lower respiratory symptoms that mark asthma; the team suggested that future projects to ease traffic congestion should include plans to monitor changes in these health effects.

Three quasi-intervention studies were performed in Germany to investigate changes in lung function and respiratory symptoms over several years as ambient TSP concentrations fell following reunification of the country (Heinrich et al., 2002; Frye et al., 2003; Suguri et al., 2006).

In two of these studies, data were collected from three consecutive cross-sectional surveys (1992–1993, 1995–1996, 1998–1999) administered to the parents of schoolchildren in three towns (Zerbst, Hettstedt and Bitterfeld). Air pollutant measurements (TSP and SO₂) were obtained from fixed ambient air monitors. From 1991 to 1998 mean annual TSP concentrations declined from 45 µg/m³ to 29 µg/m³ in Zerbst; from 64 µg/m³ to 25 µg/m³ in Bitterfeld and from 79 µg/m³ to 33 µg/m³ in Hettstedt. In addition, declines in AMP numbers and increases in NMPs were observed. Subjects who had moved from their previous home within 2 years or whose actual residence was located further than 2 km from their previous home were excluded.

In the first study, Heinrich et al. (2002) examined the prevalence of non-allergic respiratory disease in schoolchildren 5–14 years of age. Data were treated in a two-stage approach. First, Poisson GEEs were used to investigate the association between air pollution and respiratory disease. Age, gender, parental education and parental atopy, plus four indoor factors (home dampness and moulds, gas cooking, home ETS exposure and contact with cats) were included in the model as potential confounders. Secondly, adjusted prevalence logits were regressed against an air pollution variable in a mixed linear model. Possible effect modification was explored for combinations of area, survey and various potential modifiers. Continuous declines in symptom prevalence were reported for all three areas; this was clearest for bronchitis and for frequent colds. Analyses revealed that bronchitis, otitis media, sinusitis, frequent colds, febrile infections, cough in the morning and shortness of breath were all positively related to TSP exposure, though not all associations were significant. In a total exposure analysis, an increment of 10 µg/m³ in TSP was associated with an excess risk for lifetime bronchitis (24% (95% CI 11.5–39.5%)), lifetime sinusitis (20.9% (95% CI 0.00–46.1%)) and frequent colds (13.7% (95% CI 3.2–25.3%)). In children with indoor exposure factors (damp homes, moulds, gas from cooking, ETS or contact with cats), the same increase in TSP was associated with increased risk for lifetime bronchitis (21.5% (95% CI 8.2–36.7%)) as well as with frequent colds, defined as more than two in the last 2 months (12.5% (95% CI 2.1–23.7%)). In children without indoor exposure factors, the same increase in TSP was also associated with lifetime bronchitis (40.6% (95% CI 19.5–65.5%)) and frequent colds (17.5% (95% CI 0.00–37.9%)). The authors commented that similar risks for bronchitis were reported in this study and the Harvard Six Cities Study (Dockery et al., 1989), but a higher risk was reported in the SCARPOL study (Swiss Study on Childhood Allergy and Respiratory Symptoms with Respect to Air Pollution, Climate and Pollen) by Braun-Fahrländer et al. (1997).

In the second study, Frye et al. (2003) only considered sixth grade schoolchildren (11–14 years of age). Lung function was assessed with FVC and FEV₁ measurements. Linear regression analysis of lung function parameters was conducted against air pollution data with sex, height, season, lung function equipment, parental education, parental atopy and ETS included as covariates. Significant associations were observed between reductions in air pollution and lung function improvements; a 10 µg/m³ decrease in annual TSP was associated with a 0.94% increase in FVC (95% CI 0.04–1.9%). When the analysis was restricted to females, the effect was even stronger (1.2% (95% CI 0.2–2.22%)). No significant changes in FEV₁ were found. Both of these studies demonstrated that improvements in air quality can have significant, positive impacts on the respiratory health of children.

The third study (Sugiri et al., 2006) of the effects of German reunification used similar methods (consecutive cross-sectional surveys) to investigate the effect of traffic-related air pollution on respiratory lung function of children aged 5–7 between 1991 and 2000 in both rural and urban former East and West German communities. Airway resistance (R_{aw}) and total lung capacity (TLC) in children were assessed. Daily (mean values of the investigation day) and annual mean values (values of the year before) of TSP and SO₂ were determined; TSP measurements were made with a β-ray absorption sampling technique. Ambient air values were obtained from

monitoring stations located far from heavy traffic roads or from major industrial sources, to reflect large-scale urban or rural exposure (the authors mention that such stations could not adequately reflect high levels of exposure). Reductions in TSP and SO₂ ambient concentrations were observed in the study period. The annual mean for TSP in West Germany ranged from 54.35 µg/m³ to 44.20 µg/m³ between 1991 and 2000 while the annual mean for TSP in East Germany ranged from 74.45 µg/m³ to 51.29 µg/m³ between 1991 and 1997. The mean TSP levels on the day of the examination ranged from 51.01 µg/m³ to 49.75 µg/m³ from 1991 to 2000 in West Germany and from 127.9 µg/m³ to 49.65 µg/m³ from 1991 to 1997 in East Germany.

Analyses were performed using random effects models to determine the mutually adjusted association between lung function and short-term and chronic particle exposure and its interaction with living near a busy road. Children suffering from acute airway infection and from asthma were excluded, as were those living at their home address for less than 2 years. Questionnaires were completed by parents (e.g. home distance from heavy traffic roads, age, sex, height, BMI, birth weight, parental education, bedroom sharing, fossil fuels heating, gas use for cooking, smoking at home, maternal smoking during pregnancy and cold temperature (<0°) during respiratory effect investigation) and these factors were included in the model. Logarithm transformed lung function measurements were analyzed by linear regression. Differences in lung function among children living in the former East and West Germany disappeared with time as levels of TSP became more equal. In stratified analysis, an increase of 10 µg/m³ in daily TSP levels was associated with an adjusted increase of 0.6% (95% CI 0.0–2.2%) in R_{aw} in East German children living farther from busy roads (≥50 m), while no association was found in children living in West Germany. Also in children living farther from busy roads (≥50 m) an increase of 10 µg/m³ in the mean annual TSP was associated with a significant decrease of -1.8% (95% CI -3.3% to -0.3%) in TLC. A significant decrease of -1.6% (95% CI -2.3% to -0.8%) was also found in East Germany with TLC. In children living near heavy traffic roads (<50 m) in West Germany, an increase of 10 µg/m³ in the mean daily TSP was also associated with a significant reduction in TLC (-0.5% (95% CI -0.7% to -0.2%)); no significant association was found in children from East Germany. Overall, a 10 µg/m³ change in annual TSP was associated with a decrease in TLC (-1.55% (95% CI -0.01% to -2.9%); p < 0.1) while change in daily TSP, at lag 0 d, was associated with a decrease in airway resistance (-0.8% (95% CI -1.6% to -0.008%); p < 0.1). It was found in this study that TLC showed clear associations with long-term TSP levels while R_{aw} was affected by short-term levels. This study showed that better lung function was associated with reductions in TSP in East Germany. However, given the increasing effect of traffic-related pollution in East Germany, the favourable effects were presumably counteracted by elevated air pollution from increased traffic.

14.5.6.3 Summary and Considerations: Intervention Studies

Intervention (or accountability) studies attempt to evaluate the impacts of actions (policy-related, planned, unplanned or “natural” interventions) taken to improve air quality. There is a growing body of evidence that suggests immediate health benefits accrue from air pollution control measures. Few intervention studies were identified in the recent literature; these studies investigated the impacts of various actions taken to reduce air pollution levels (implementation of air pollution abatement measures, construction of a road bypass to ease traffic congestion, reunification of Germany) on several health outcomes. These studies showed improvement in lung function and respiratory symptoms as pollution levels decreased. A diminution in overall mortality in relation to long-term exposure to PM_{2.5} was also noted in a re-analysis of data from the Harvard Six Cities Study.

Similarly to other types of epidemiological studies, intervention studies have limitations in their study designs (small reductions in the air pollutants, reductions/changes only applicable for a small population that will result in limited statistical power, confounding factors). The

interventions that have been studied are so varied it is not possible to compare effects across the limited number of studies. However, these unique studies contribute to the epidemiological evidence of adverse health effects from air pollution, as they can demonstrate health improvements following changes in air pollution levels. Improvements in air quality have been shown to include reductions in both respiratory illness and death, in children and adults.

14.5.7 Source Apportionment Studies

The application of techniques to apportion air pollution health effects among various sources of PM is relatively new. This section focuses on the results of studies in which source apportionment was applied to health effects analyses. A broader discussion of source apportionment is found in Section 14.1.7.3.

Recognizing the need to understand how source apportionment was being applied to health effects analyses and wanting to compare different apportionment techniques, the US EPA sponsored a workshop on this topic in 2003. Teams of investigators from seven centres (nine analyses per city) applied various multivariate factor source apportionment techniques to two sets of PM_{2.5} speciation data (Washington, DC, and Phoenix, AZ). Each set of results was then analyzed using city-specific time-series mortality generalized linear models adjusted for weather, seasonal/temporal trends and day-of-the-week at various lags. From these results, variance-weighted average risk estimates were calculated to summarize the variability between investigators and/or methods.

14.5.7.1 Study Results

The data available from Washington and Phoenix differed in several ways, though the conclusions reached after comparing the results from different models and/or investigators were similar. Daily speciation data were available for Phoenix, whereas similar data for Washington were only obtained from monitors on Wednesdays and Saturdays. The Washington data covered the years 1988–1997, whereas the Phoenix data were limited to 1995–1997. The mortality data in Phoenix were limited to individuals ≥ 65 years of age, but similar restrictions were not applied to the Washington data.

In Washington, all teams and methods identified factors for soil, traffic and SS, while other factors were only identified by some teams: nitrate ($n = 7$), residual oil ($n = 6$), primary coal ($n = 3$), wood smoke ($n = 5$), sea salt ($n = 5$) and incinerators ($n = 4$). Soil, traffic, SS and nitrate accounted for more than 80% of PM_{2.5}; SS was estimated to make up as much as 60% of the PM_{2.5} mass. Using 5th–95th percentiles of source-apportioned PM_{2.5} (considered more relevant to assessing risk for low- and high-level pollution and accounting for potential bias in measurements compared with an 'x' $\mu\text{g}/\text{m}^3$ approach), few significant positive effects on total mortality were reported at lags between 0 and 4 d, with the exceptions of SS (lag 3 d) and the related factor, primary coal (lag 3 d). Total PM_{2.5} was associated with total mortality in a similar fashion to SS. The soil factor was associated with smaller RRs, which were consistently positive but not significant across all lags. No clear patterns of effects were observed for any of the other source-apportioned factors. Results for cardiovascular and cardiorespiratory mortality (data not presented for the latter) were similar in pattern, but with fewer significant risk estimates than for total mortality. Sulphate is less influenced by exposure misclassification than other sources (more uniformity across areas vs. sources such as traffic or incinerators that are expected to be more locally dispersed), which may help to explain why it, but not other factors, was significantly associated with mortality. Sensitivity analyses were conducted with different weather models and it was concluded that while most point estimates were similar to the baseline model,

different models (defined by different smoothing terms and degrees of freedom) influenced the lag structure of effects (e.g. for sulphate) (Ito et al., 2006).

The factors identified in analyses of the Phoenix data were soil/crustal, traffic, SS, biomass/wood combustion, sea salt (marine) and copper smelter. Soil, traffic and SS factors were better correlated across investigators and/or methods than biomass/wood combustion. Consistently positive associations (in decreasing relative magnitude) were observed between cardiovascular mortality and the 5th-to-95th-percentile increase in PM_{2.5} source apportioned to SS, traffic and copper smelter-derived particles at lag 0 d, 1 d and 0 d, respectively. Total PM_{2.5} (measured by TEOM or gravimetrically) was associated with cardiovascular mortality in a similar manner as the combined traffic factor, which explained a large fraction of the total PM_{2.5}. The sea salt factor appeared to have an increasing association with cardiovascular mortality, with RR that was consistently negative but non-significant at early lags (potentially due to residual confounding, over-fitting or sharing of effects by correlated variables) and only positively significant at lag 5 d. Fine particle soil and biomass burning/wood combustion factors were not associated with total or cardiovascular mortality. In contrast to the results from Washington, effects on total mortality were weaker, often negative and mostly non-significant compared with the results for cardiovascular mortality. For example, associations of total mortality with copper smelter were smaller but still positively significant, whereas most SS associations lost significance and direction. Some of these differences may be related to contrasting levels of pollutants between the two cities (e.g. higher SS levels in Washington) (Mar et al., 2006).

Several similarities were noted between the results and conclusions of the analyses of data from both cities. The lag structures of association were similar across investigators and methods but different across source factors. This made it more difficult to compare results between source factors. It was suggested that different lags could indicate different mechanisms of action for different sources and it was also highlighted that single lag studies may underrepresent effects for some factors. The Washington analyses were also limited by 2-day-a-week speciation data, which made it difficult to evaluate effects on consecutive days and which may have influenced the lag structures of effect. In both cities the results of analysis of variance (ANOVA) tests used to study the variability in results suggested that lag day and pollution source factor explained more of the variability in risk estimates than investigators and/or methods. More of the variability was also observed to be due to standard regression error than to the investigator or method.

While results from both cities consistently suggested that variability between results was less an issue of methodology than either source factor or lag, several areas of future research were suggested. First and foremost, these authors suggested that although there was consistency across their results, this did not preclude the need for future testing of the accuracy of source apportionment results (the apportioned mass concentrations). In particular, Ito et al.(2006) recommended that more analyses of speciation data using cities with larger populations are needed. Several other areas were identified for future research: testing of the sensitivity of results to different models, the separation of diesel from spark-ignited traffic (only two teams did so for the current analyses), the different lag structures of different source factors, and differential exposure misclassification across source types. The authors also noted the need to address questions related to variations in correlations with weather/temporal trends across source factors and how this variability may affect model sensitivity to specific factors or influence lag structures for different source factors, and the need to conduct multi-city studies, especially across cities with different dominant sources (Mar et al., 2006; Ito et al., 2006).

A limited number of other source apportionment studies have examined health effects related to air pollution. Two panel studies (Lanki et al., 2006b; Penttinen et al., 2006) were conducted in

Helsinki, Finland, under the auspices of the ULTRA project to assess the cardiovascular and respiratory effects of source-derived PM_{2.5} particles on subjects with pre-existing conditions.

In the first study principal component analysis was applied to a 6-month analysis of exercise-induced ischemia in non-smoking older adults with stable CHD (n = 45, 21 females, mean age of 68 years). Measurements of PM_{2.5} were apportioned into factors of crustal, LRT, oil combustion, salt and local traffic. Multi-pollutant models were constructed that included elements as surrogates for sources instead of source-apportioned mass; for every source the element with the highest correlation with source-specific mass was chosen as the source indicator. The following pairings of source indicators and factors were identified: Si and crustal; S and LRT; Ni and oil combustion; Cl and salt; and absorbance (ABS) and local traffic. A 1 µg/m³ increase in PM_{2.5} attributed to LRT and in PM_{2.5} attributed to local traffic was associated with ST-segment depressions >0.1 mV at lag 2 d. When a stricter criterion was used (ST-segment depression >0.1 mV with horizontal or downward slope) these effects remained, and the authors also noted suggestive evidence of an association with PM_{2.5} attributable to oil combustion. In the multi-variable models including indicator elements for all factors, only ABS (local traffic) was associated with ST-segment depressions (both criteria at lag 2 d). In single-pollutant models, UFPs had been associated with depressions >0.1 mV; however, in a two-pollutant model only the effect of ABS remained significant. Overall, results from this study suggested that fine combustion particles (mainly from traffic) may be responsible for exercise-induced ST-segment depressions in older adults with CHD (Lanki et al., 2006b).

In the second study the relationships between source-specific PM_{2.5} and elemental components of PM_{2.5} and changes in ΔPEF (deviation from mean PEF) and respiratory symptoms (cough, asthma symptoms, medication use) were studied in a cohort of adult asthmatics (n = 57, mean age of 53 years, 44 females) using lags 0–3 d and a 5-d mean for analyses. Using principal component analysis the authors identified the following sources: local combustion (Cu, Zn, Mn, Fe), LRT (S, K, Zn), soil-derived particles (SiO₂, Al, Ca, Mn, Fe), oil combustion (V, Ni), sea salt (Na, Ca) and unidentified sources. The most consistent association was between PM_{2.5} attributed to local combustion and declines in ΔPEF. Decreases were observed in the morning and afternoon using a 5-d mean average, as well as in the evening at lag 1 d. PM_{2.5} from LRT was only associated with reduced ΔPEF in the morning (lag 1 d). Levels of PM_{2.5} attributed to soil were generally associated with changes in the opposite direction at all time points (positive, significant associations at lag 0 d, and generally positive, but non-significant associations at lags 1 and 2 d and a 5-d average) and the factors oil, salt and unidentified sources were not associated with changes in ΔPEF. Associations between the factors and cough, asthma prevalence or medication use were generally weak or non-significant. A decrease in asthma symptom prevalence was reported at lag 3 d in association with PM_{2.5} attributable to LRT. Some negative, but usually non-significant, associations were observed between the factors of local combustion, oil combustion and sea salt and medication use. Elemental components of PM_{2.5} were not associated with changes in ΔPEF, medication use, asthma symptoms or cough. Overall, these results suggested that the negative effects of PM_{2.5} on changes in ΔPEF in adult asthmatics were primarily mediated through particles attributed to local combustion sources (Penttinen et al., 2006).

Riediker et al. (2004b) applied principal factor analysis to apportion estimated risks from a small panel study of nine on-the-job healthy male state troopers (Riediker et al., 2004a) to specific sources using two models. The first model included PM_{2.5} components and gaseous pollutants that were correlated with PM_{2.5}. The second model was more restrictive, excluding components with large uncertainties. This resulted in factors defined as soils, automotive steel wear, gasoline combustion and speed-changing traffic for the first model and soil and road surfaces, gasoline combustion and speed-changing traffic for the second model. The authors proposed

that the dominant components of the speed-changing traffic factor were indicative of brake wear (Cu), engine emissions (aldehydes) and possibly, secondary urban particles. In both models the strongest associations with health outcomes were with the speed-changing traffic factor. In the first model, this factor was associated with increases in blood urea nitrogen, mean red cell volume, percentage of neutrophils and vWf as well as decreases in percentage of lymphocytes and protein C, in addition to increases in mean cycle length of normal R-R intervals, SDNN, pNN50 and supraventricular ectopic beats. The pattern of effects associated with a factor by the same name in the second model was the same as that of the first model. While not identical, the speed-changing traffic factors in each model were dominated by Cu, S and aldehydes and were highly correlated with each other ($r = 0.91$). Associations with other factors were limited to the first model and included increases in uric acid and mean cycle length with the crustal factor and increases of mean cycle length with the gasoline factor.

Schreuder et al. (2006) examined the association of $PM_{2.5}$ and $PM_{2.5}$ chemical speciation collected at a residential monitoring site in Spokane, WA, between 1995 and 2002 in relation to ERVs for respiratory diseases. Three multivariate receptor algorithms were applied for chemical speciation and eight $PM_{2.5}$ sources were identified, including vegetative burning, As-rich, motor vehicle, sulphate aerosol, nitrate aerosol, airborne soil, Cu-rich and marine. Positive but non-significant associations were found between $PM_{2.5}$ and ERVs for respiratory diseases at lags 0 and 1 d that were higher during the heating season than the non-heating season. Results from $PM_{2.5}$ chemical speciation provided evidence that ERVs for respiratory diseases were significantly associated with an IQR of $3.0 \mu\text{g}/\text{m}^3$ in $PM_{2.5}$ from vegetative burning (RR = 1.023 (95% CI 1.009–1.088) at lag 1 d). Vegetative burning was a dominant contributor to $PM_{2.5}$ during the winter heating season (due to woodstove use) and a higher RR was observed in the winter season (RR = 1.051 (95% CI 1.010–1.094) at lag 1 d). Positive but non-significant results were also observed for As-rich, motor vehicle and airborne soil components.

14.5.7.2 Summary and Considerations: Source Apportionment Studies

The application of source apportionment techniques to the air health effects literature is relatively new. It has been applied to time-series and panel study analyses of various endpoints in different types of subjects. The validity of these types of studies was strengthened by the outcomes of an EPA-sponsored workshop, in which multiple analyses of $PM_{2.5}$ speciation data from two different cities by seven teams were applied to mortality data. The conclusions reached after comparing these different results suggested that source apportionment in health effects analysis is fairly robust. Results across investigators and methods and variations in results between investigators and/or methods were less than variations across source categories or lags. The strongest associations in these studies were between mortality and SS, which as a regional pollutant may lend itself to less exposure misclassification than other factors. In general, associations with total mortality were greater than cardiovascular mortality in the Washington analyses, and the opposite was observed in the Phoenix analyses. There was greater variability between groups with respect to attributing $PM_{2.5}$ to traffic as a result of greater variability in defining this factor. By contrast, the results from other recent source apportionment studies suggested a role for traffic-related factors with respect to changes in HRV, inflammatory parameters, exercise-induced ST-segment depressions and changes in ΔPEF , as well as a role for vegetative burning with ERVs for respiratory diseases.

Although the results of the EPA-sponsored workshop highlighted the consistency among investigators and/or methods, Ito et al. (2006) cautioned that this does not guarantee the accuracy of the apportionment, and noted that more research is required to further our understanding of the sources and factors that contribute to the health effects associated with exposure to $PM_{2.5}$. The health outcomes that have been studied are so varied it is not possible to compare similar effects across different studies. In addition, the diversity of geographic

settings and sources (which can be more limited in single-city studies) adds to the difficulty of evaluating consistency across the limited number of available studies. Growing interest in this area of research should help to address this gap.

14.6 Epidemiology Studies of Developmental and Reproductive Endpoints

Potentially adverse developmental and reproductive effects resulting from exposure to air pollution have only recently been investigated. Several hypotheses have been proposed to explain the biological mechanisms that may underlie air pollution-related changes in birth outcomes. These include changes to the pituitary–adrenocortico–placental system, changes in uterine blood flow, maternal infections, abnormal placental development, acute and chronic inflammation, decreased supplies of oxygen and nutrients to the placenta, DNA damage and oxidative stress. These mechanisms may work synergistically or may be causally interrelated.

14.6.1 Summary of Previous Assessments

Previous assessments by Health Canada and the US EPA have, to varying degrees, assessed the potential developmental and reproductive effects of exposure to PM. No studies on these topics were identified in the 1999 PM SAD. Studies reviewed by the US EPA 2004 PM AQCD indicated mixed results with respect to postnatal mortality, intrauterine growth retardation (IUGR), LBW and preterm birth. No reproductive studies were identified. Positive, and sometimes significant, associations between PM₁₀ and respiratory postnatal mortality or sudden infant death syndrome (SIDS) in American cities were compromised by lack of control for co-pollutants and possible interrelationships between pollutants and other factors (e.g., sociodemographics). Suspended particles were associated with respiratory mortality in single- and multi-pollutant models in the Czech Republic, and in Mexico City the strongest association with infant mortality in multi-pollutant models was with PM_{2.5}; however, the applicability of these findings to the US was not clear. The only studies of IUGR were conducted in the Czech Republic. Exposures to PM_{2.5} and PM₁₀ in the first month of gestation were associated with IUGR; in a later study, exposure to PM was also associated with IUGR, but only in a highly polluted city, and not in a city with low pollution. In the only LBW study, the authors concluded there was no overall association with PM₁₀ although a significant association was observed in the Hispanic subpopulation. Stronger effects were observed with gaseous pollutants (CO and SO₂). Little weight was given to a significant finding between TSP/SO₂ and very low birth weight (VLBW) because direct pollutant measurements were not made. Finally, PM₁₀ was associated with preterm birth in one study, but no associations were observed in a second American study. The need for further research, including studies that controlled for well-established links to fetal growth and development, was highlighted.

14.6.2 Birth Outcomes

The recent literature (published since 2002) included investigations of several well-defined endpoints, including infant mortality, premature births (<37 weeks gestation), LBW (<2500 g), reductions in absolute body weight, small for gestational age (SGA) (birth weight <10th percentile for gestational age) and IUGR (<10th or <15th percentile of predicted birth weight based on gestational age and sex in term infants). Fewer studies of birth defects and reproductive endpoints were identified.

14.6.2.1 Infant Mortality

Infant mortality studies published since 2002 were limited. Seven studies were identified; among them, two originated from North America, one from Europe, three from Asia, and one was a global meta-analysis.

Dales et al. (2004) conducted a time-series study to compare daily air pollution concentrations with SIDS incidence in 12 Canadian cities, using data from 1984 to 1999. No significant associations were observed between PM₁₀ or PM_{2.5} (mean 24-h concentrations: 23.43 µg/m³ and 12.27 µg/m³, respectively) and the incidence of SIDS (data not presented), although significant positive associations were observed with gaseous pollutants (SO₂, NO₂ and CO).

In contrast, a California case-control study (1:10 ratio) noted that a 10 µg/m³ increase in PM₁₀ 2 months before death was associated with all-cause post-neonatal death between 1989 and 2000 in infants 4–12 months in a single-pollutant model (OR = 1.04 (95% CI 1.01–1.06)). This relationship was even stronger in infants exposed to ≥75th percentile of PM₁₀ (>54.1 µg/m³) (OR = 1.14 (95% CI 1.03–1.27)); however, these results lost significance, but remained positive, in multi-pollutant models with CO, NO₂ and O₃. Respiratory post-neonatal deaths were also associated with a 10 µg/m³ increase in PM₁₀ 2 weeks before death for infants aged 28 d–1 year (OR = 1.05 (95% CI 1.01–1.10)) and 4–12 months (OR = 1.12 (95% CI 1.02–1.23)), and were again stronger with exposure to higher concentrations of PM₁₀ (>56.0 µg/m³; OR = 1.46 (95% CI 1.13–1.88) and OR = 1.41 (95% CI 1.02–1.96) for 28 d–1 year and 4–12 months, respectively). The only association with respiratory mortality to remain statistically significant in multi-pollutant models was between PM ≥56.0 µg/m³ and post-neonatal deaths 28 d–1 year (OR = 1.40 (95% CI 1.03–1.89)). These results remained consistent among LBW and/or preterm infants. In fact, the association with respiratory mortality was stronger in these subgroups, although the sample numbers were small and estimates imprecise. Associations with SIDS followed a similar pattern to all-cause mortality but were non-significant. Positive, significant findings were also reported for the gaseous pollutants CO and NO₂, but not O₃ (Ritz et al., 2006).

The results of other studies have limited application to Canadian exposure situations, due to high concentrations of PM, less relevant metrics of particulate exposure or statistical limitations. In a time-series study of temperature and air pollution in Madrid, Spain, TSP was associated with daily mortality in children <10 years at lags 0 and 1 d in single and multi-pollutant models, with stronger associations at concentrations greater than 100 µg/m³ and in the summer. When the results were stratified by age, stronger signals were apparent in subjects aged 1–5 years compared with those of 0–1 year (Diaz et al., 2004). In case-crossover analyses, PM₁₀ (daily concentrations, approximately 20–230 µg/m³) was positively, but not significantly, associated with post-neonatal mortality in Taiwan (Tsai et al., 2006a; Yang et al., 2006). In a time-series analysis that was limited by the use of GAMs, PM₁₀ (24-h average concentration: 69.2 ± 31.6 µg/m³) was also associated with total and respiratory mortality in Korean children 0–2 years (Ha et al., 2003). In a quasi-meta-analysis of five studies conducted in Mexico City, Seoul, South Korea, the Czech Republic and the US, PM₁₀ was associated with post-neonatal all-cause mortality (acute and chronic exposure) and respiratory mortality (Lacasana et al., 2005).

14.6.2.2 Premature (Preterm) Births

Data on the fetal effects of acute exposure to air pollution during pregnancy are limited. Reportedly the first time-series study of the association between air pollution and preterm birth was conducted by Sagiv et al. (2005) using data from four Pennsylvania counties covering the years 1997–2001. In contrast to most other birth outcome studies, which considered potential chronic effects on the fetus and spatial gradients of exposure, this study was an investigation of the effects of exposure to air pollution (PM₁₀, CO, NO₂ and SO₂) in the 6 weeks prior to birth. The 6-week average of PM₁₀ was 27.1 ± 8.3 µg/m³, and daily PM₁₀ averaged 25.3 ± 14.6 µg/m³. Marginal associations between a 50 µg/m³ increase in PM₁₀ and preterm birth (<36 weeks gestational age) were observed in 6-week, 2-d and 5-d lag models (RR = 1.07 (95% CI 0.98–1.18); RR = 1.10 (95% CI 1.00–1.21); and RR = 1.07 (95% CI 0.98–1.18), respectively).

The majority of preterm birth studies investigated associations with longer-term exposures to ambient PM. In a Vancouver study of data from 1985 to 1998, it was reported that no associations were observed between PM₁₀ and preterm births (data not presented), but significant positive associations were observed with the gaseous pollutants SO₂ and CO. However, the available PM₁₀ data were limited to five years, and sulphur oxides may be a good indirect measure of exposure to fine respirable PM (Liu S et al., 2003).

In a Brisbane, Australia, retrospective cohort (2000–03), a 4.5 µg/m³ increase in PM₁₀ in the first, but not the second or third trimester, based on city-wide averages of five monitors ($r = 0.80-0.93$), was associated with preterm birth (OR = 1.15 (95% CI 1.06–1.25)). This association was strongly driven by the effect in the first month of pregnancy (OR = 1.19 (95% CI 1.13–1.26)), and a significant increasing trend was observed across quartiles of PM₁₀ exposure in the first trimester ($p < 0.001$) (Hansen et al., 2006). Similar, but non-significant results of smaller magnitudes were presented for bsp (visibility reducing particles, PM_{0.1-2.5}). Evidence of a non-significant, protective association with bsp during the 3 months of the last trimester was dismissed by the authors as an artifact that lacked biological plausibility. When first-trimester PM₁₀ and ozone were modelled together, neither pollutant was significantly associated with preterm birth (OR = 1.09 (95% CI 0.98–1.22) and OR = 1.16 (95% CI 0.98–1.39), respectively). This may be expected, as the monthly associations with preterm birth across the first trimester trended upwards for ozone and downwards for PM₁₀. This observation may also suggest different mechanisms of action for each pollutant. The average daily PM₁₀ concentration was 19.6 ± 9.4 µg/m³.

Weak and inconsistent associations have been observed across other cohort studies. In a study in Southern California which expanded on previous work (e.g. Ritz and Yu, 1999; Ritz et al., 2000, 2002), PM₁₀ and PM_{2.5} were not significantly associated with preterm births in single- or multi-pollutant models (the latter with CO, NO₂, and O₃), except for an association with PM_{2.5} 6 weeks before birth at PM_{2.5} concentrations ≥ 24.7 µg/m³ using a single-pollutant ZIP-code level model (OR = 1.19 (95% CI 1.02–1.40)). For the first trimester, third trimester and 6 weeks before birth, 24-h pollutant averages (with range) were 42.2 µg/m³ (26.3–77.4 µg/m³), 41.5 µg/m³ (25.7–74.6 µg/m³) and 39.1 µg/m³ (13.0–103.7 µg/m³), respectively, for PM₁₀ and 21.9 µg/m³ (11.8–38.9 µg/m³), 21.0 µg/m³ (11.8–38.9 µg/m³) and 21.0 µg/m³ (9.9–48.5 µg/m³), respectively, for PM_{2.5}. Similarly to LBW results reported elsewhere in this document, small sample sizes (approximately 100–700 cases for PM_{2.5} and 400–3,000 cases for PM₁₀) contributed to wide confidence intervals and marginally significant results. It is worth noting that borderline positive associations were observed with PM₁₀ (first trimester and 6 weeks before birth) which decreased as distance to monitor increased. While some marginal associations were also associated with PM_{2.5} 6 weeks before birth, negative associations were more frequent between exposure in the first trimester and preterm birth. In multi-pollutant models these negative associations became positive, but not significant (data not presented). Co-linearity between pollutants and smaller samples as a result of fewer days of PM_{2.5} data contributed to unstable multi-pollutant models. Associations with CO were strongest near CO-only monitors (Wilhelm and Ritz, 2005).

In a previous case-control study by the same authors in Los Angeles, CA (1994–96), an association between distance-weighted traffic density (DWTD) and preterm birth was observed, but no associations were observed between annual background concentrations of PM₁₀, NO₂, or O₃ and preterm birth. A significant positive association was observed with CO. Quartiles of annual PM₁₀ were <36.19 µg/m³, 36.19–41.11 µg/m³, 41.12–42.78 µg/m³ and ≥ 42.79 µg/m³ (Wilhelm and Ritz, 2003). In another study from California in which an air pollution index was developed as the primary exposure metric using data from 1998–1999, preliminary analyses did not reveal any associations between either preterm births or SGA births and individual

pollutants (PM₁₀, CO, NO₂, SO₂, O₃), although the authors noted that a more thorough analysis was required. Pollution concentrations and individual pollutant associations were not presented (Woodruff et al., 2003).

In a California case-control study (1999–2000), each preterm birth (<36 weeks) was matched to three term births of 39–44 weeks gestation (those of 37–38 weeks were excluded to create a buffer of distinction between term and preterm). A 10 µg/m³ increase in PM_{2.5} (measured at the nearest monitor within 5 mi (8km) of mother's address at time of birth) was associated with preterm birth when the highest quartile (>22.1 µg/m³) was compared with lowest across total, first month, and last 2 weeks of gestation (OR = 1.15 (95% CI 1.07–1.23), OR = 1.21 (95% CI 1.12–1.30) and OR = 1.17 (95% CI 1.08–1.26), respectively). Similar results were also observed in the third quartile of exposure, in the second quartile for the first month and last 2 weeks of gestation, and when exposure was characterized in a continuous fashion. Dose–response trends were apparent for total gestation and first month, but these trends were not tested for significance. Results were very similar after adjusting for CO (little to no change in magnitude or significance). No significant results were observed for CO; however, unlike PM_{2.5}, maternal addresses were not matched to CO monitors due to small sample size (Huynh et al., 2006).

In a case-control study, data from the Georgia Very Low Birth Weight Study (1986–1988) were extracted and compared with two measures of ambient PM₁₀ (residence in a county with or without an industrial point source of PM₁₀, and modelled concentration of PM₁₀ at home using an atmospheric transport model). When preterm/AGA (appropriate birth weight for gestational age) deliveries (cases, n = 59) were compared with term/AGA deliveries (controls, n = 197), the adjusted ORs for maternal residence in a county with a PM₁₀ point source and for exposure to the annual modelled upper quartile (>15.07 µg/m³) vs. first quartile (<1.48 µg/m³) PM₁₀ were OR = 4.31 (95% CI 1.88–9.87) and OR = 3.68 (95% CI 1.44–9.44), respectively. The odds were greater that infants were born preterm VLBW (AGA or SGA) (n = 128) than term/AGA (n = 197) when mothers resided in counties with a point source of PM₁₀ (OR = 2.54 (95% CI 1.46–4.22)). No significant effects were observed by quartile of PM₁₀ exposure (<1.48 µg/m³, 1.48–3.74 µg/m³, 3.75–15.07 µg/m³ and >15.07 µg/m³), though the association for the fourth quartile of exposure was almost significant (OR = 1.94 (95% CI 0.98–3.83)). The lack of term/SGA infants in this study was identified as a gap. The authors concluded that the association between air pollution and LBW may be partially explained by the length of gestation (preterm vs. term) (Rogers and Dunlop, 2006).

In a Korean study conducted under ambient conditions that are poor surrogates for Canadian exposure (the upper and lower bounds of average daily PM₁₀ quartiles were 26.99 and 106.39 µg/m³, and 33.12 and 95.91 µg/m³ for the first and third trimesters, respectively), preterm delivery was associated with PM₁₀ in the first trimester, but no trend across quartiles of exposure was observed (Leem et al., 2006).

14.6.2.3 Birth Weight

Only two Canadian epidemiological studies of birth weight published in the review period were identified. In a study of deliveries in Nova Scotia between 1988 and 2000, LBW was associated with exposure to PM₁₀ (fourth vs. first quartile; average 24-h concentration 17 µg/m³) during the first, but not second or third, trimester of singleton births to mothers residing within 25 km of a NAPS monitor, at ≥37 weeks gestation (RR = 1.33 (95% CI 1.02–1.74)). After adjusting for birth year this association lost significance (RR = 1.11 (95% CI 0.84–1.48)). With respect to other pollutants, a dose-dependent relationship was observed between SO₂ (a potential indirect indicator of fine PM) and LBW during the first trimester (Dugandzic et al., 2006). In the other Canadian study, the authors reported that no associations were observed between PM₁₀ and LBW (data not presented) in infants born in Vancouver between 1986 and 1998. The authors

suggested this may have been due to a limited number of measurements for PM₁₀ (1994–1998 vs. 1985–1998 for other pollutants) and fewer live births during this period. A significant positive association was observed with SO₂ (perhaps an indirect measure of fine respirable PM) but not other gaseous pollutants (CO, NO₂, O₃). Live births were excluded from analyses if birth weight was less than 500 g (Liu S et al., 2003).

In a 2005 study by Wilhelm and Ritz, which expanded on previous work (Ritz and Yu, 1999; Ritz et al., 2000, 2002), a 10 µg/m³ increase in PM₁₀ was associated with an increased risk of LBW (OR = 1.22 (95% CI 1.05–1.41)) in the third trimester when maternal residence was ≤1 mi (1.6 km) from a monitoring station. This risk increased in multi-pollutant models with CO, NO₂ and O₃ (OR = 1.36 (95% CI 1.12–1.65)) but decreased as distance of maternal residence to monitor increased and was marginally significant in ZIP-code-level analysis (OR = 1.03 (95% CI 0.97–1.09)). Risk estimates observed across the entire pregnancy were smaller than third-trimester point estimates and not significant in multi-pollutant models (OR = 1.24 (95% CI 0.91–1.70); single-pollutant results not presented). No associations were observed with PM_{2.5}, but the authors attributed this to fewer years of monitoring data (1999–2000 vs. 1994–2000 for other pollutants). The strongest significant associations were observed with CO, but these were generally limited to maternal residences near monitors that only measured CO. The authors concluded that local heterogeneity, specifically from traffic-related pollutants, may have influenced the results of this study.

In a subset of subjects from the CHS in California, PM₁₀ was not significantly associated with LBW, though OR were non-significantly increased in the second and third trimesters, and for the entire pregnancy. Average monthly 24-h values of PM₁₀ were 45.8 ± 12.9 µg/m³, 46.6 ± 15.9 µg/m³, 45.4 ± 14.8 µg/m³ and 45.4 ± 15.5 µg/m³ for the entire pregnancy, first trimester, second trimester and third trimester, respectively. No significant associations with O₃, NO₂ or CO were observed. The authors suggested that LBW may not be the best outcome to measure if not very prevalent in the population, as was the case in this study (72 cases, among 3,901 children born between 1975 and 1987) (Salam et al., 2005).

In a meta-analysis that included only five studies from China, the Czech Republic and the US published between 1994 and 2003, a 10 µg/m³ increase in PM₁₀ (TSP data converted to PM₁₀ for three studies; presented as annual or average third trimester exposure) was associated with a marginal increase in LBW (1.6% (95% CI 1.0–2.2%)). Data were not reported for other exposure windows (first or second trimester). A similar positive but non-significant association was observed with SO₂, whereas a much stronger significant association was observed with CO (Lacasana et al., 2005).

The assessment of declines in birth weight measured as absolute change in weight (as opposed to categorical analysis using the definition of LBW) was limited to a few studies in the recent literature. In an Australian study (1998–2000) the strongest significant associations were observed with NO₂, especially when analyses were limited to the second trimester for mothers residing within 5 km of a monitor. Daily PM₁₀ and PM_{2.5} concentrations averaged 16.8 ± 7.1 µg/m³ and 9.4 ± 5.1 µg/m³, respectively. Exposure to 1 µg/m³ PM_{2.5} in the month before birth and the second trimester was more strongly associated with declines in birth weight than was PM₁₀ (-2.48 g (95% CI -4.58 g to -0.38 g) and -4.10 g (95% CI -6.79 g to -1.41 g), respectively, vs. -1.21 g (95% CI -2.31 g to -0.11 g) and -2.05 g (95% CI -3.36 g to -0.74 g), respectively). However, in analyses limited to babies born to mothers residing within 5 km of a monitor, significant declines in birth weight were more strongly associated with PM₁₀ across all windows of exposure, while positive and negative non-significant associations were observed with PM_{2.5}. For these later analyses, the associations with PM₁₀ and NO₂ remained significant in two-pollutant models (with O₃, CO or each other) and after controlling for exposures in other

pregnancy periods, but not in a four-pollutant model; stronger declines were associated with NO₂ than with PM₁₀ (Mannes et al., 2005).

In California (1999–2000), for infants delivered at 40 weeks gestation for whom monitoring information was available within approximately 5 mi (8 km) of the mother's residence, the difference in mean birth weight between highest and lowest quartile of PM_{2.5} exposure (>18.4 µg/m³ vs. <11.9 µg/m³) was -36.1 g (95% CI -16.5 g to -55.8 g). Similar results were observed when CO was adjusted for and when data were considered by individual trimester. No significant changes were observed with CO; the direction of results was mixed after adjusting for PM_{2.5} (Parker et al., 2005). In contrast, stronger associations were observed with ozone (dose–response relationship) and CO in a subset of subjects (n = 3,901) from the CHS born between 37 and 44 weeks gestational age. A significant association with 20 µg/m³ PM₁₀ in the third trimester (-21.7 g (95% CI -42.2 to -1.1 g)) was reduced and no longer statistically significant in a multi-pollutant model with ozone (-10.8 g (95% CI -31.8–10.2 g) (Salam et al., 2005).

In contrast to Mannes et al. (2005), the results of sensitivity analyses to assess the effect of distance between maternal residence and pollution monitor (Basu et al., 2004) indicated that risk estimates were not increased with increasing proximity to the monitors. In this California study, neighbourhood (monitors within 5 mi (8 km) of maternal residence) and county (average of all monitors in the county of maternal residence at the time of birth) exposures were correlated ($r^2 = 0.77–0.78$), but their associations with birth weight were slightly stronger in relation to county-wide PM levels in first-time, married mothers 20–30 years of age who had at least a high school education. Average daily PM_{2.5} concentrations based on 9-month gestational averages were 15.8 ± 4.9 µg/m³ (monitors 0–5 mi (0–8 km)) 15.6 ± 3.7 µg/m³ (county monitors) and 14.5 ± 5.3 (monitors 0–1 mi (0–1.6 km)) µg/m³ for non-Hispanic white women and 18.2 ± 5.0 µg/m³, 16.9 ± 3.3 µg/m³, and 16.4 ± 5.4 µg/m³, respectively, for Hispanic mothers. Using county-level exposure data, a 1 µg/m³ increase in total gestation PM_{2.5} was associated with similar reductions in birth weight in both the non-Hispanic white and Hispanic populations (-4.04 g (95% CI -6.71 g to -1.37 g), and -4.35 g (95% CI -7.47 g to -1.23 g), respectively). When neighbourhood PM_{2.5} concentrations were used, significant results were only observed for the Hispanic population (-2.49 g (95% CI -4.53 g to -0.45 g)) but differences between the two groups were not statistically significant. When data were restricted to mothers living within 1 mi (1.6 km) of a monitor, the risk estimates were similar to those for the neighbourhood PM_{2.5} concentrations, but no associations reached significance, perhaps because sample sizes were much smaller (~10% of study population). The authors noted that it was unclear whether neighbourhood or county-level monitoring data better predicted personal exposure to PM_{2.5}. They suggested that county-level data, for which stronger associations were observed in both groups, may have correlated more with maternal personal exposure, as neighbourhood-level data assume women spend most of their time at or near their home, which may not be true (Basu et al., 2004).

Several studies identified in the literature published after 2002 were conducted at ambient PM exposures much higher than those usually observed in Canada (24-h PM₁₀ > 40 µg/m³; personal PM_{2.5} = 43.1 µg/m³). Changes in PM₁₀ or personal PM_{2.5} were associated with LBW in Sao Paulo, Brazil, Krakow, Poland, and Seoul, South Korea. In all three studies, co-linearity with either CO or ETS made interpretation of the results difficult (Lee BE et al., 2003; Gouveia et al., 2004; Jedrychowski et al., 2004). In Taiwan, reduced birth weight was significantly related to PM₁₀ in one study (Yang et al., 2003), whereas in another study LBW was not associated with PM₁₀ (Lin et al., 2004). In both studies, there was a significant association with SO₂, a potential indirect measure of fine respirable PM, and neither study conducted analyses with both pollutants simultaneously.

14.6.2.4 Small for Gestational Age and Intrauterine Growth Reduction

Three studies (one case-control, two cohorts) evaluated the SGA endpoint. This endpoint is considered by some to be less restrictive than LBW, which may be hard to interpret, as birth weight is influenced by both length of gestation and rate of growth (Woodruff et al., 2003). In general, associations of SGA with PM were observed across studies of very different designs.

In one California study, analyses were limited to births at 40 weeks' gestation to mothers who resided within 5 mi (8 km) of a monitor. When subjects exposed to the highest quartile of 9-month $PM_{2.5}$ ($>18.4 \mu\text{g}/\text{m}^3$) were compared with the lowest quartile ($<11.9 \mu\text{g}/\text{m}^3$), the OR for SGA was only significant when adjustment was made for CO (1.23 (95% CI 1.03–1.50)). This association decreased with trimester, remaining significant for each, but a trend analysis was not presented. Similar results were observed in an analysis that controlled for distance between mother's residence and nearest monitor (Parker et al., 2005). In the second study, in Sydney, Australia, births were not limited by gestational age; significant associations with $1 \mu\text{g}/\text{m}^3$ $PM_{2.5}$ (all births: OR = 1.03 (95% CI 1.01–1.05)) and $1 \mu\text{g}/\text{m}^3$ PM_{10} (mothers' residence within 5 km of a monitor: OR = 1.02 (95% CI 1.01–1.03)) were limited to the second trimester. The latter association was non-significant when exposure to PM_{10} during other periods of pregnancy was controlled for. Stronger associations were observed with NO_2 (Mannes et al., 2005).

In a case-control study, data from the Georgia Very Low Birth Weight Study (1986–1988) were extracted and compared against two measures of ambient PM_{10} (residence in a county with or without an industrial point source of PM_{10} , and modelled concentration of PM_{10} at home using an atmospheric transport model). To assess the association between air pollution and IUGR, preterm/AGA infants ($n = 59$) were compared with preterm/SGA infants ($n = 69$). There was no significant association between PM_{10} and the risk of SGA among preterm infants, although the modelled pollutant results suggested a positive dose–response association across quartiles of PM_{10} exposure. Quartiles of PM_{10} exposure ranged from $<1.48 \mu\text{g}/\text{m}^3$ to $>15.07 \mu\text{g}/\text{m}^3$ (Rogers and Dunlop, 2006).

The term IUGR refers to diminished fetal growth rates, and while related, is not the same as SGA. However, based on this similarity and the fact that the terms are sometimes used interchangeably, results for IUGR are presented here. There was some variation in the definitions of IUGR used in the three identified studies. Canadian studies used a cut-off of the 10th percentile of predicted birth weight, while an American study used the 15th percentile. A study in three Canadian cities (Montreal, QC, Calgary and Edmonton, AB) was limited to live births between 37 and 42 weeks of gestation. A $10 \mu\text{g}/\text{m}^3$ increase in $PM_{2.5}$ (24-h average $12.2 \mu\text{g}/\text{m}^3$) in a single-pollutant model was associated with similar significant increases in IUGR (OR ~ 1.06) for each trimester of pregnancy. However, in a three-pollutant model, significant effects were associated with CO, but not with NO_2 or $PM_{2.5}$ (Liu et al., 2007). In an earlier Vancouver, BC, study (1985–1998), there was no association between IUGR and PM_{10} (no data were presented) and the authors suggested that the lack of association with IUGR may have been due to a limited number of PM_{10} measurements (fewer days of sampling and only 5 years of data) (Liu S et al., 2003). In a study of a subset of subjects from the CHS (585 of 3,901 had IUGR) PM_{10} (24-h average of the entire pregnancy: $45.8 \pm 12.9 \mu\text{g}/\text{m}^3$) was not associated with IUGR. ORs were at or slightly above unity for all pollutants (O_3 , NO_2 , CO and PM_{10}) and none of the confidence intervals excluded unity (Salam et al., 2005).

14.6.2.5 Other Birth Outcomes

Other birth outcomes have been evaluated in a limited number of studies. A case-control study (2:1 ratio for the largest case group) of the relationship between air pollutants (PM_{10} , O_3 , NO_2 , SO_2 and CO) and eight clinical diagnostic groups of isolated or multiple birth defects in seven Texas counties between 1997 and 2000 was designed to confirm the findings of an earlier

California study (Ritz et al., 2002). However, the two studies used different windows of exposure (mean of gestational weeks vs. gestational months), which may have contributed to the differences in observed outcomes. In the earlier study, the primary associations with birth defects were attributed to exposure to ozone and CO, not PM₁₀. In the more recent study similar magnitudes of association were observed, but birth defects (comparing upper quartiles with the referent first quartile of exposure) were related to PM₁₀. An increasing trend of atrial septal defects was associated with PM₁₀, while associations with pulmonary artery atresia without ventricular septal defects were observed in the second and third quartiles of exposure. Only a suggestive association with isolated cleft lip (with or without cleft palate) was reported. In addition, associations were observed with the gaseous pollutants CO (tetralogy of Fallot and multiple conotruncal defects) and SO₂ (isolated ventricular septal defects and all ventricular septal defects combined). Pollutant data were collected for weeks 3–8 of pregnancy, and PM₁₀ quartiles were defined as <19.5 µg/m³, 19.5 – <23.8 µg/m³, 23.8 – <29.0 µg/m³ and ≥29.0 µg/m³ (Gilboa et al., 2005).

In a study that employed GAMs in statistical analyses, mothers in Krakow, Poland, were exposed to personal PM_{2.5} (measured over 2 d in the second trimester) that ranged from 10 to 147 µg/m³ (mean = 43 µg/m³). It was observed that infants born to mothers exposed to higher concentrations of personal PM_{2.5} had shorter mean length and smaller head circumference than infants of mothers exposed to lesser concentrations (Jedrychowski et al., 2004). These findings are consistent with associations between exposure to PM and measures including LBW, SGA and IUGR reported in a number of studies summarized in previous sections.

14.6.3 Reproductive Effects

In the sole recent study relating a reproductive endpoint to measures of air pollution, no association was observed between PM₁₀ (lag 0–9, 10–14, or 70–90 d) and semen quality in 5,134 semen samples (from 48 Los Angeles sperm donors, 1996–1998). Average daily PM₁₀ concentrations were 35.47 ± 13.83 µg/m³, based on 1-in-6-day sampling. The only significant change in sperm concentration was associated with ozone; no effects were observed with NO₂ or CO (Sokol et al., 2006).

14.6.4 Summary and Considerations: Epidemiology Studies of Developmental and Reproductive Endpoints

Several studies have contributed to the relatively new but growing literature on adverse birth outcomes associated with exposure to air pollution. Studies (primarily case-control and cohort) of the fetal effects of longer-term (e.g. averaged over the trimester) rather than acute exposure to air pollution predominate in the literature. The exposure metrics used in these studies have included PM₁₀, PM_{2.5} and proximity to industrial sources.

Studies reviewed by the US EPA 2004 PM AQCD indicated some evidence among a limited number of studies of PM-related effects on postnatal mortality, preterm birth and LBW. The more recent literature reviewed in this assessment generally provides additional support for the association of PM with these categories of effect. However, the number of studies remains limited, the findings are not entirely consistent, and there are important uncertainties with respect to the possible role of co-pollutants, the appropriate measure of exposure to PM, and critical periods of exposure during pregnancy.

In the US EPA 2004 PM AQCD, positive, and sometimes significant, associations between PM₁₀ and respiratory postnatal mortality or SIDS in American cities were observed, but were limited

by a lack of control for co-pollutants and possible interrelationships between pollutants and other factors (e.g. sociodemographics), and significant findings in other countries were considered of uncertain applicability to the US. In the limited more recent literature reviewed in this assessment, there were fairly consistent positive associations between total and respiratory postnatal mortality, which were most often statistically significant. However, though the associations with PM were robust to adjustment for other pollutants in some studies, and some co-pollutants (e.g. SO₂) may be indirect measures of exposure to fine PM, there still remains some question about the possible role of other pollutants (which were often more consistently and/or more strongly related to mortality) in these PM-related effects.

At the time of the US EPA 2004 PM AQCD, PM₁₀ had been associated with preterm birth in one of two American studies. Recent cohort and case-control studies have furthered our understanding of this association. Overall, associations with preterm births were positive (sometimes non-significant); positive associations were more often observed in areas with higher PM₁₀ concentrations (e.g. fourth quartiles rather than referent first quartiles of exposure) and in early or late pregnancy (first month or last 6 weeks of pregnancy). In some studies in which no positive, significant findings were observed, sample sizes were small, PM data were limited or the focus of the studies was not on individual pollutants. In the first reported time-series study of the effects of acute exposure to air pollution, there was a borderline association between preterm birth and PM₁₀ levels 2d, 5d and 6 weeks prior to birth.

In the single study of birth weight reviewed by the US EPA 2004 PM AQCD, the authors concluded there was no overall association with PM₁₀, although a significant association was observed in a Hispanic subpopulation and stronger effects were observed with gaseous pollutants (CO and SO₂). In newer studies reviewed in this assessment, exposure to PM₁₀ or PM_{2.5} was associated with declines in birth weight (either categorical, as defined by LBW, or as a decrease in absolute weight in grams) in the majority of studies. The associations between PM and LBW or declines in birth weight appeared to be stronger in the third trimester than in other periods of pregnancy in several studies. While distance-to-monitor analyses were similar to the main estimates in some studies, spatial variability was observed in others. Stronger associations were observed at the highest quartiles of exposure in two studies, fraction-dependent effects were sometimes observed when the mother's residence was <5 km from a monitor, and in one study associations were stronger with county-level exposures than with neighbourhood-level exposures. The authors of the latter study argued that it is unclear whether county-level or neighbourhood-level exposures best depict personal exposures (neighbourhood levels are only more appropriate if women spend most of their time at home, and this assumption has not been validated). When gaseous pollutants were measured, associations were stronger for one or more of these pollutants compared with PM in all but one study, although in several studies the association was with SO₂, which may be an indirect indicator for fine PM.

A limited number of investigations of other endpoints, including IUGR, SGA, birth defects and reproductive endpoints, preclude drawing any conclusions about their associations with exposure to air pollution. At the time of the US EPA 2004 PM AQCD, the only studies of IUGR were conducted in the Czech Republic, and no studies of SGA, birth defects or reproductive endpoints were identified. Exposures to PM_{2.5} and PM₁₀ in the first month of gestation were associated with IUGR, and in a later study exposure to PM was also associated with IUGR, but only in a highly polluted city. In more recent studies reviewed for this assessment, exposure to PM_{2.5} was associated with IUGR in one Canadian study, but two studies from Vancouver and California did not find a similar link to PM₁₀ exposure. The lack of association observed in Vancouver may have been partially attributable to a lack of PM₁₀ data, while in the California study slightly positive but non-significant results were observed for all pollutants. The results of

studies of associations between PM and SGA were somewhat more consistent. $PM_{2.5}$ was associated with SGA in two studies, and in a third study, while PM_{10} was not significantly associated with SGA, there was an apparent dose–response link across quartiles of PM_{10} . In one of these studies a significant association with $PM_{2.5}$ was only observed in the second trimester, and was weaker than the association with NO_2 , whereas in the second the effect was only significant when adjusted for CO but appeared to decline over semester (no trend analysis presented). The study of other endpoints has been limited in the recent literature. Selected birth defects were associated with PM_{10} in one study, in contrast to a similar earlier study in which gaseous pollutants (but not PM_{10}) were associated with birth defects. In the only reproductive study, semen quality was not associated with PM_{10} .

It is not yet clear which are the most important spatial and temporal exposure windows for the adverse outcomes observed. In general, there have been very few endpoints associated with exposure during the second trimester of pregnancy, while stronger associations were more notable in the early first trimester and in the third trimester. With respect to fetal growth, these periods correlate with implantation and formation of the placenta, which occurs in the first trimester, and weight gain, which occurs primarily in the third trimester. These results narrow the expected critical temporal window, but more research is needed to further define the most important periods of exposure during pregnancy.

With respect to spatial variability, the majority of studies used mother's residence at time of birth to determine exposures to air pollutants. This is consistently acknowledged as a weakness of this type of study, as it cannot account for residential moves during pregnancy or day-to-day movements of expectant mothers. Results were mixed in sensitivity analyses that addressed which distance to monitor best characterized maternal exposure. In some studies, stronger associations were observed using county-level exposures, while the results of other studies indicated that the RRs increased as distance to monitor decreased.

Other common limitations of such studies include lack of control for maternal smoking status and limited monitoring data. However, authors indicated several reasons why smoking may not have confounded the observed results: they included doubts about the correlations between smoking and the time patterns observed for pollution associations, and a suggestion that smoking would not differentially influence one metric over another in studies that compared different PM metrics (e.g. neighbourhood vs. county).

Current evidence suggests that both PM and gaseous pollutants such as CO (a marker for traffic) may be linked to adverse birth outcomes; however, more research is necessary to clarify these associations. There are biologically plausible explanations for the observed effects of CO. For example, in its review of ozone, the US EPA (2006) suggested that CO may cause effects by crossing the placental barrier and binding with fetal haemoglobin. In the recent literature there were often stronger associations with CO than with other pollutants. More robust associations were observed for CO than PM_{10} for IUGR, preterm births and LBW. There are not enough data to determine the relative strengths of association between $PM_{2.5}$ or CO, if the observed effects of CO lose significance after controlling for $PM_{2.5}$ or if results are dependent on study design. Many studies cited limited PM data as a weakness of their research. Given time, more $PM_{2.5}$ monitoring data will become available from national monitoring networks, which in turn should reduce this weakness and help to address the issue of relative associations between CO and $PM_{2.5}$. Variations in associations with different pollutants may also be related to seasonal differences (lack of adjustment for season was a weakness identified in the US EPA 2006 Ozone AQCD); however, the majority of recently published papers did adjust for season.

14.7 Epidemiology Studies of Genetics

14.7.1 Summary of Previous Assessments

No studies of the genetic effects of, or genetic susceptibility to, fine PM were identified in the 1999 PM SAD. At the time of the US EPA 2004 PM AQCD there were only limited data on genetic susceptibility or DNA damage, and these results were primarily toxicological studies. Studies in humans were limited to investigations of mutagenicity and DNA adducts after exposure to residential woodsmoke or occupational exposure to diesel exhaust. In one study, differential effects were not observed when genetic polymorphisms (GSTM1 *null* and NAT2 (N-acetyltransferase 2) slow acetylators) were considered. The US EPA concluded that “the extent to which genetic susceptibility plays a role in humans remains to be determined.”

There has been increased interest in the study of the potential genetic damage caused by exposure to air pollution. In addition, other recent studies have investigated genetic subpopulations that may be more susceptible to the effects of air pollution.

However, while there is a growing body of literature with respect to genetic susceptibility to ozone-related effects, there were only limited data on genetic susceptibility or DNA damage associated with fine PM, and these results were limited primarily to toxicological studies. The study of genetically susceptible populations has been limited to a small number of studies of older adult male Americans and asthmatic children in Mexico City.

In a cross-sectional study, 497 older male participants of the Normative Aging Study in Boston, MA, were assessed to determine whether there was a gene–environment interaction between variants (C282Y and H63D) of the hemochromatosis gene HFE, which is responsible for Fe absorption, and changes in HRV associated with exposure to air pollution (mean 48-h moving averages of PM_{2.5} and BC were $11.7 \pm 7.8 \mu\text{g}/\text{m}^3$ and $0.92 \pm 0.46 \mu\text{g}/\text{m}^3$, respectively). No changes in HRV were observed when HFE variant was considered as a binary factor (either HFE variant present or absent). When PM_{2.5} and HFE variant were modelled together as main effects, decreases in HF were associated with a 48-h moving average of PM_{2.5}. In a subsequent model an interaction between HFE variant and PM_{2.5} on HF was reported ($p = 0.02$); the interaction was even stronger in a sensitivity analysis of only subjects without IHD. When HFE variants were stratified, an association between HF and a $10 \mu\text{g}/\text{m}^3$ change in PM_{2.5} was only observed in subjects with the wild-type HFE gene (-31.7% (95% CI -10.3% to -48.1%). Changes in SDNN, LF and LF/HF were reported to be similar, but no data were reported. A similar, but non-significant pattern (stronger effects in wild-types) was also observed after exposure to BC (Park et al., 2006).

In a second cross-sectional analysis of subjects from the same study, the effects of PM_{2.5} (mean 48-h moving average: $11.4 \pm 8.0 \mu\text{g}/\text{m}^3$) on HF measurements were found to be greater in subjects with the GSTM1 *null* genotype (-34% (95% CI -9% to -52%) vs. -27% (95% CI -8% to -42%) in all subjects) for a $10 \mu\text{g}/\text{m}^3$ increase in PM_{2.5}). When stratified by GSTM1 status and statin use, this decline in HF was only observed in subjects not taking statins who were genotyped GSTM1 *null* (-34% (95% CI -53.0% to -7.20%)). Non-significant but positive trends were observed towards a greater decrease in HF in obese subjects and subjects with high neutrophil counts who lacked the GSTM1 gene, as opposed to subjects with the GSTM1 gene (Schwartz et al., 2005b).

In the only other population studied for genetic susceptibility to the effects of air pollution, 151 asthmatic children residing in Mexico City were genotyped for GSTM1 and GSTP1. With respect to lung function, no susceptible groups were identified, but bronchodilator use was only

associated with PM₁₀ at lags 1, 2 and 6 d in subjects genotyped GSTP1 Val/Val. Average 24-h PM₁₀ and 1-h max PM₁₀ were 56.68 ± 27.36 µg/m³ and 137.42 ± 78.67 µg/m³, respectively (Romieu et al., 2006).

A series of Scandinavian studies found that personal exposure to PM_{2.5} or UFPs was associated with DNA damage. In an equal number of healthy male and female subjects, DNA oxidative damage (8-oxodG) was associated with personal PM_{2.5} (median 16.1 µg/m³) and BC (8.1 x 10⁶/m) (Sørensen et al., 2003a, 2003b). In a later study, DNA damage (8-oxodG) was also associated with personal PM_{2.5} (median in fall: 20.7 µg/m³, median in summer: 12.6 µg/m³) and its components, V and Cr (Sørensen et al., 2005b). Cumulative indoor, cumulative outdoor, and personal exposures to UFPs while cycling (13.4–32.4 x 10⁻³ UFPs/mL) in Copenhagen, Denmark, were associated with purine oxidation, measured by formamidopyrimidine glycosylase (Fpg)- sensitive sites, a marker for DNA damage. No associations were observed, however, with fixed-site measurements of UFPs or PM₁₀ (Vinzents et al., 2005).

Although there has been a substantial increase in research on the effects of exposure to air pollution on markers of DNA damage, several of these were not designed to include measures of PM (e.g. comparing “low” and “high” pollution areas) and are therefore not included in this assessment. In a pilot study, the association between personal exposure to air pollution and DNA damage, as measured by the Comet assay, was compared between groups of indoor and outdoor workers in two Mexican cities. Positive findings were only observed in outdoor workers in Mexico City. In this group, exposure to personal occupational PM_{2.5} (133 µg/m³) was associated with high DNA damage (≥60% cells with longer tails) (OR = 1.02 (95% CI 1.01–1.04)) (Tovalin et al., 2006). In a case-control study nested in the European Prospective Investigation into Cancer and Nutrition (EPIC) study, which appeared to lack appropriate adjustment for meteorological variables, a 1 µg/m³ increase in annual average PM₁₀ (1992–1994) was not correlated with DNA adducts (Peluso et al., 2005).

14.7.2 Summary and Considerations: Genetics

Data are inadequate to draw conclusions on DNA damage resulting from exposure to PM. The recent literature was primarily limited to studies of healthy subjects in which DNA oxidative damage was associated with personal exposures to UFP, PM_{2.5} and BC, and less associated with fixed-site measurements. In support of proposed mechanisms of action involving oxidative stress, there was some limited evidence that subjects genotyped GSTM1 *null* experienced greater declines in HF after exposure to air pollution than did subjects genotyped GSTM1 *wt*. Other potentially susceptible groups that were identified included HFE *wt* and GSTP1Val/Val genotypes; however, data to support these results were even more limited.

While there has been some indication that particular genetically defined subgroups experience greater effects as a result of exposure to air pollution, more research is needed to complement these initial studies. Similarly, there is recent evidence that exposure to PM results in oxidative DNA damage, but this research needs to be supported by work in other environments by other groups using study designs that allow for review of pollutant-specific associations.

It should be noted that none of the studies quoted address the issue of the proportion of the population impacted by the specific genetic polymorphisms. For example, in the study of HFE variants in relation to PM exposure, only 14/518 were homozygous for the minor allele and only 0.6% for the CC allele for C282Y. As a consequence of these low frequencies, in conjunction with the rather imprecise results, it is uncertain whether these findings will have much impact in free-living populations.

14.8 Chronic Exposure Epidemiology

Although a variety of study designs have been used to study the health effects associated with long-term exposure to air pollution, most of the more recent studies are based on cohorts of individuals enrolled in a database in order to study their health relationships with a variety of risk factors (e.g. smoking, lifestyle). These studies focus on the individual and the factors altering individual risk that can be examined to provide information on group risk. In most available studies, exposure to air pollution is estimated as the concentrations measured at air monitoring stations established to monitor compliance with ambient air quality targets. In some studies, however, the exposure metric is somewhat more refined, such as through modelled estimates of outdoor pollution at each individual's residence.

The cohort studies on which the ascertainment of chronic effects is based have the advantage of incorporating extensive information on individual risk factors that can be examined in addition to the risk of air pollution over time. Additionally, because of their long-term (or "longitudinal") structure, these studies make it possible to estimate the life-shortening impact of an individual risk factor such as air pollution. However, longitudinal cohorts are relatively rare due to their considerable financial and logistical requirements. Additionally, because many of the outcomes associated with air pollution are also associated with other risk factors (e.g. cardiovascular disease is associated with smoking and with diet), extensive analyses are required to distinguish air-pollution-related effects.

Both short- and long-term studies provide information on the magnitude of risk from air pollution exposure. Their results are likely additive—the mortalities observed in one type of study are not accounted for in the other—and can provide information on susceptibility by examining all-cause, respiratory, cardiovascular and other causes of death, as well as through age-specific analyses. However, long-term cohort studies are regarded as more robust and informative because they can account for other risk factors and because of the inherent follow-up time periods, which allow examination of important issues such as length of life lost.

14.8.1 Mortality Studies

14.8.1.1 Summary of Previous Assessments

A major concern identified in the 1999 PM SAD was that most of the previous long-term effect studies used cross-sectional designs, which cannot infer a causal relationship since no information is available on the time sequence of exposure and outcome. However, two cohort studies substantially improved our knowledge of PM long-term mortality effects: the Harvard Six Cities Study (Dockery et al., 1993) and the ACS Study (Pope et al., 1995). As part of the Harvard Six Cities Study, Dockery and collaborators followed a cohort of 8,111 adult subjects in the northeast and midwest United States for 14–16 years beginning in the mid-1970s. The risk estimates for all-cause mortality comparing the least polluted with the most polluted city were associated with differences in ambient fine particles and SO_4^{2-} concentrations of $18.6 \mu\text{g}/\text{m}^3$ and $8.0 \mu\text{g}/\text{m}^3$, respectively. Higher $\text{PM}_{2.5}$ and SO_4^{2-} levels were both found to be associated with increases in all-cause mortality (13% for $\text{PM}_{2.5}$ (95% CI 4–23%) and 33% for SO_4^{2-} (95% CI 10–61%) per $10 \mu\text{g}/\text{m}^3$) when comparing the most polluted with the least polluted city. An increase in fine particles was also associated with increased mortality from cardiopulmonary disease, and with a non-significant increase in lung cancer mortality. In the much larger ACS Study, Pope et al. (1995) followed 552,138 adult subjects in 154 US cities from 1982 through 1989. Again, higher ambient levels of fine particles were associated with increased all-cause and cardiopulmonary disease mortality in the 50 cities for which fine particle data were available

(sampled from 1979–1983). Higher ambient SO_4^{2-} levels were associated with increased mortality from all causes, cardiopulmonary disease, and lung cancer in the 151 cities for which SO_4^{2-} data were available (sampled from 1980–1982). The differences between all-cause mortality in the most polluted and the least polluted cities were 7% (95% CI 4–10%) per $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ and 7% (95% CI 4–11%) per $10 \mu\text{g}/\text{m}^3$ SO_4^{2-} . Multi-pollutant models were not included in either of these studies.

Lung cancer is manifested only after a long latency period, and is generally considered to result from a multi-step process leading to a chronic condition. In both of the above prospective cohort mortality studies (Harvard Six Cities and ACS), lung cancer rates in cities with more air pollution were higher than rates observed in less polluted cities, and were about the same when regressed against a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ (Dockery et al., 1993) or SO_4^{2-} (Pope et al., 1995). These results gave limited support for a role of PM in eliciting lung cancer.

Newer studies reviewed in the US EPA 2004 PM AQCD included a comprehensive reanalysis (Krewski et al., 2000) of the Harvard Six Cities and ACS studies to validate the original studies and to test the robustness of the original analyses with alternate risk models and analytic approaches, new analyses of the AHSMOG (Adventist Health Study on the Health Effects of Smog) cohort, and data from a cohort of veterans. Reanalyses of the Harvard Six Cities and ACS studies confirmed the original investigators' findings of associations between mortality and long-term exposure to PM. This study recognized, however, that increased mortality may be attributable to more than one ambient air pollution component.

Based on an evaluation of all the available long-term studies, the US EPA 2004 PM AQCD attributed the greatest weight to the results of the Harvard Six Cities and ACS studies, which were also supported by the findings of other new long-term studies. The Harvard Six Cities and ACS studies included measured PM data and relatively representative study populations; in addition, their results had been validated through an exhaustive reanalysis (Krewski et al., 2000, 2005). One new effect reported in the extended analysis of the ACS Study (Pope et al., 2002) was a statistically significant association between fine particle and SO_4^{2-} concentrations (previously noted just with SO_4^{2-}) and lung cancer mortality (14% (95% CI 4–23%) per $10 \mu\text{g}/\text{m}^3$ increases in $\text{PM}_{2.5}$, using air quality data averaged across all available years. This effect estimate remained stable and significant after adjustment for covariates (age, sex, race, smoking, education, marital status, body mass, alcohol consumption, occupational exposure and diet), random effects modelling and spatial smoothing methods. (As discussed in the US EPA 2004 PM AQCD, there was some support for this finding in the AHSMOG cohort, in which lung cancer mortality in males was increased, although not significantly, in relation to fine PM (39% (-21–146%) per $10 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$, and to a lesser degree with coarse PM (26% (95% CI -38%–156%) (McDonnell et al., 2000)). Based on the revised ACS studies, effect estimates for deaths from all causes fell in a range of 6–13% per $10 \mu\text{g}/\text{m}^3$ of $\text{PM}_{2.5}$, while effect estimates for deaths from cardiopulmonary causes ranged from 6% to 19%. In addition, it was concluded that the extended analyses of the ACS Study did not reveal an association between chronic exposure to thoracic coarse particles and mortality. With respect to the shape of the relationship between mortality and PM, the US EPA 2004 PM AQCD reported that using flexible spline modelling Krewski et al. (2000) found a visually near-linear relationship between all-cause and cardiopulmonary mortality residuals and mean SO_4^{2-} concentrations, and between cardiopulmonary mortality and mean $\text{PM}_{2.5}$. However, the curve between all-cause mortality residuals and mean $\text{PM}_{2.5}$ concentrations flattened above approximately $20 \mu\text{g}/\text{m}^3$.

The US EPA 2004 PM AQCD concluded that recent long-term exposure studies confirmed the limited evidence available in the US EPA 1996 PM AQCD indicating that long-term PM exposure was linked with mortality. A number of analyses using data from the ACS cohort have shown significant associations of fine PM and/or sulphates with both total and cardiopulmonary

mortality, and some have also reported significant associations with lung cancer mortality. At that time, however, it was impossible to draw conclusions regarding the possible effects of long-term exposures to UFPs, given the paucity of relevant data.

14.8.1.2 Total Mortality

A total of 10 new chronic mortality studies published between 2002 and 2006 have been reviewed in this assessment. Eight studies were conducted in North America, while two were performed in Europe. These analyses were carried out under various climate conditions, using different approaches and statistical models. All studies except one (Lipfert et al., 2006) used only single-pollutant models. PM_{2.5} was used in six studies; other PM metrics that were used were BS, PM₁₀ and TSP.

Two studies with a focus on TSP were conducted in Hamilton, ON. From 1992 through 1999, Finkelstein et al. (2003) examined the associations between non-accidental mortality, household income and air pollution in a cohort of people with respiratory problems aged >40 years. Postal codes were used to assess household income (by linking with census data), and exposure was estimated using TSP ambient monitoring data and a Geographic Information System (GIS) to estimate air pollution levels at the residence of each subject. Cox proportional hazards regression models were adjusted for pulmonary function, BMI and diagnoses of chronic disease. Compared with people in the most favourable category (higher incomes with lower particulate levels), the highest mortality risk levels were observed among individuals with low income and exposure to high pollution levels. Increased risks for all-cause mortality were 33% (95% CI 12–57%) for the high income–high pollution group (\$64,000 average household income; average TSP = 46 µg/m³), 82% (95% CI 30–155%) for the low income–low pollution group (\$34,000 average household income; average TSP = 37 µg/m³) and 162% (95% CI 67–313%) for the low income–high pollution group. An age effect analysis for TSP data revealed a decreasing risk with increasing age for all-cause mortality (-4% (95% CI -6% to -1%) with an interaction term for age. In each group, positive and significant associations were also observed between all-cause mortality and SO₂ (high income–high pollution, 35% (95% CI 5–73%), low income–low pollution, 64% (95% CI 21–124%) and low income–high pollution, 140% (95% CI 61–258%).

The other Canadian study (Jerrett et al., 2005a) used a cross-sectional design to study the impact of PM on 1985–1994 mortality in Hamilton while controlling for other confounding factors such as household income, education level or work-related exposure (occupation type). Again, exposure was estimated using TSP data from ambient monitors interpolated and using kriging (a geostatistical technique). Air pollution data were coupled to geocoded mortality data to obtain a risk unit and comparative mortality figures (CMFs) were then calculated. CMF is a statistical tool used to standardize census-tract data with whole-city data to allow comparison between the two. A sensitivity analysis was done with standardized mortality ratios (SMRs) to evaluate the validity of using CMFs, since they are recognized as being unstable when data numbers within strata are low. Comparative mortality figures were regressed on TSP values and sociodemographic variables using weighted least squares while independent variables were regressed on CMFs. After converting TSP to PM_{2.5} (using a 25% ratio of PM_{2.5} to TSP based on an assessment of 1999 pollution data supplied by the Ontario Ministry of the Environment) a 10 µg/m³ increase in annual PM_{2.5} equivalent was associated with an increased risk of 59% (95% CI 26–101%) in non-accidental mortality in women; the estimate for men was 80% (no CIs were reported). Including socioeconomic confounders in the model reduced the risk estimates to 27% (95% CI -8–73%) in women and 34% (95% CI 14–59%) in men. As mentioned by the authors, these risk estimates were much higher than the risk estimate found in the ACS Study of Pope et al. (2002) (6% (95% CI 2–11%)) for comparable increases in fine PM.

Four new studies conducted in the United States (Abrahamowicz et al., 2003; Enstrom, 2005; Jerrett et al., 2005b; Krewski et al., 2005) assessed the mortality risk associated with exposure to long-term air pollution. These were all extensions or subanalyses of the original ACS or Harvard Six Cities studies. Abrahamowicz et al. (2003) explored the shape of the exposure–response relationship for fine PM and sulphates, using ACS data from approximately 1.2 million adults collected between 1982 and 1989. Employing a more flexible version of the Cox proportional hazard model in which low-order polynomial regression splines are used to model possible non-linear associations, two different approaches (modified case–cohort and pooled results of 10 disjoint random subsets) were used to estimate the associations between average concentrations of fine PM (50 cities) and SO_4^{2-} (151 cities) and mortality, allowing for modelling of time-dependent and non-linear effects simultaneously. Age, lifetime exposure to smoking, obesity and education were controlled for. Both fine PM and SO_4^{2-} were associated non-linearly with mortality. The association between mortality and $\text{PM}_{2.5}$ was stronger in the lower range of concentrations ($\sim <16 \mu\text{g}/\text{m}^3$) than in the upper range of levels. The hazard ratio in the case–cohort analysis was 1.4 for a $10\text{--}16 \mu\text{g}/\text{m}^3$ increase in median $\text{PM}_{2.5}$ for the period 1979–1983 with a lower 95% CI of 1.2 (no upper CI given), with no apparent threshold below which effects were not observed. Similar analyses for SO_4^{2-} suggested that increases in sulphate levels up to $12 \mu\text{g}/\text{m}^3$ had little or no impact on the risk for all-cause mortality, but that higher concentrations were related to increased mortality; however, the authors cautioned against inferring the existence of a threshold from this preliminary finding.

Krewski et al. (2005) completed an extended reanalysis of the ACS cohort using an additional 10 years of mortality data, new pollutant data, improved control for occupational exposure and inclusion of dietary variables. The analysis was performed using the latest developments in statistical models with random effect and nonparametric spatial smoothing in the Cox proportional hazard model. The new model included covariates for marital status, smoking and education. An increase of $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ was associated with an increased risk of 7% (95% CI 4–10%) for all-cause mortality. Mortality was also analyzed for coarser size fractions (e.g. $\geq \text{PM}_{10}$) and showed a weaker, less consistent association with mortality. Among the gaseous pollutants analyzed (NO_2 , O_3 , SO_2 and CO) only SO_2 was significantly associated with mortality, including mortality not related to cardiopulmonary disease or lung cancer.

Two other studies used Californian data (Enstrom, 2005; Jerrett et al., 2005b) and proportional hazard regression models to estimate the relationship between chronic PM exposure and mortality. Enstrom (2005) examined the effect of PM from 1973 to 2002 on residents (mean age of 65 years in 1973) of 25 counties. Subjects were enrolled in 1959 in a state cohort that was part of the cancer prevention study initiated by the ACS Study. Pollution data were obtained from the California Environmental Protection Agency for the 1979–1983 period; no routinely measured $\text{PM}_{2.5}$ data were available for California before 1979 or between 1984 and 1998. However, California State fine PM measurements were resumed in 1999. The county-level average fine PM was assumed to represent $\text{PM}_{2.5}$ exposure for the entire study period for living subjects on January 1st 1973. Mortality data through 1972 were confirmed by death certificate; later mortality data were obtained from computerized registry databanks. Cohort follow-up was done in 1961, 1963, 1965, and 1972 with short questionnaires administered to survivors, and a two-page questionnaire was used in 1999. Proportional hazard regression models were used for county of residence mortality risk assessment. Control was made for the following factors: age, sex, cigarette smoking (reported in the 1959 and 1972 questionnaires), race, education, marital status, BMI, occupational exposure, exercise and diet. For total mortality, an increase of $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ was associated with an increased risk of 4% (95% CI 1–7%) for the 1973–82 period, 0% (95% CI -2–2%) for the 1983–2002 period and 1% (95% CI -1–3%) for the entire study period. No significant mortality risk was found when counties with the highest $\text{PM}_{2.5}$ levels were compared with counties having lower concentrations of $\text{PM}_{2.5}$. No higher risk was reported

in specific subgroup analyses except in smokers, where significant associations were observed. The authors acknowledged some uncertainties regarding the methodological aspects of this research, including omission of some potential confounders and the use of ambient monitors to determine exposure information; however, the impracticalities of long-term individual exposure measurements were also mentioned.

In Los Angeles, CA, Jerrett et al. (2005b) investigated the effects of intra-urban air pollution on mortality using Cox proportional hazard regression models with spatial clustering at the ZIP code area. The research assumption was that assessing air pollution burden using a community-based pollutant average could provide an underestimation of risk because of variations in levels within a community. All-cause mortality, and IHD, cardiopulmonary and lung cancer mortality were investigated using a subset of the ACS data. Universal kriging with multiquadratic models was chosen to interpolate PM_{2.5} data, and a sensitivity analysis was conducted to test this choice. Individual confounders (a standard set of 44 variables, including lifestyle, dietary, demographic, occupational and educational factors) as well as ecologic variables that included income and education level, population size and racial composition, income disparity and racial composition were controlled for in the analysis. An increased risk of 24% (95% CI 11–37%) was calculated for all-cause mortality with an increase of 10 µg/m³ PM_{2.5}; this effect remained significant after adjustment for the standard set of 44 covariates (17% (95% CI 5–30%)). When these results were compared with earlier analyses using between-community contrasts, the health effects were nearly three times greater for this analysis with a better exposure measure (i.e. 16% versus 6% in earlier analyses that controlled for the same confounders). The effects also retained significance when some ecologic variables used to control for contextual neighbourhood confounding (including income, income inequality, education, population size, racial composition, and unemployment) were considered. However, risks were reduced and became non-statistically significant with a risk estimate of 11% (95% CI -1–25%) after all eight ecological variables were included in the model. A 10 µg/m³ increase in PM_{2.5} adjusted for individual confounding factors, including proximity to freeways (500 m), was associated with an increased risk of 17% (95% CI 5–31%) for all-cause mortality. Corresponding risk estimates were higher for certain more specific causes of death, including IHD (38% (95% CI 11–72%)), lung cancer (46% (95% CI -1–116%)), endocrine (149% (95% CI -2–532%)), diabetes (82% (95% CI -45–502%)) and digestive (120% (95% CI 11–337%)). When PM_{2.5} was modelled with individual confounding variables and ozone (average of four highest 8-h maxima), associations were similar in magnitude, with a total mortality increased risk of 18% (95% CI 6–32%).

An extension of the Harvard Six Cities Study of Dockery et al. (1993) was performed by Laden et al. (2006) using 1979–1998 data. This study aimed to confirm previous findings after adding new data, as well as to look at the effect of reductions in fine PM concentrations as a result of control measures. Mortality RRs were obtained using Cox proportional hazard models, taking into account smoking status, education and BMI; subjects were stratified by sex and age in 1-year increments. Reduction in annual mean PM_{2.5} concentrations across all cities and diminution in overall mortality were observed during the study period. A reduction of 10 µg/m³ PM_{2.5} was associated with a decreased risk of -27% (95% CI -43% to -5%) in total mortality when comparing PM_{2.5} average levels between the 1990–1998 and 1980–1985 periods; the corresponding figures for cardiovascular and respiratory mortality were -31% (95% CI -54–10%) and -57% (95% CI -84–13%), respectively. This study revealed that a 10 µg/m³ increase in annual PM_{2.5} was associated with increased risks of 17% (95% CI 8–26%) and 13% (95% CI 1–27%) for the 1974–1989 and 1990–1998 periods, respectively. For the entire period (1974–1998), a 16% (95% CI 7–26%) increased risk was observed; it decreased when mean annual city-specific PM_{2.5} (concentration in the year of death) was considered (14% (95% CI 6–22%)). Finally, cardiovascular mortality was positively associated with PM_{2.5} over the entire study

period, with a greater risk estimate than that for total mortality (28% (95% CI 13–44%)), while a non-significant association was observed for respiratory mortality (8% (95% CI -21–49%)). This new evidence from the Harvard Six Cities Study cohort revealed a relatively large reduction in risk estimate for mortality associated with decreases in PM_{2.5}.

Finally, one study was conducted by Lipfert et al. (2006) using the Veteran cohort data for the period 1997–2002. Additional PM_{2.5} data were obtained from ambient monitors (sampled for 24 h every sixth day), using both TEOM and gravimetric method measurements. Proportional hazard regression models were used for data treatment, comparing values of air quality/traffic predictors based on the maximum variation in mortality that could result from a change in concentration of specific pollutants following extreme pollution control measures (designated as “achievable” effects). This team also looked at the association between mortality and several metals and other PM constituents. Non-statistically significant associations were observed between mortality and PM_{2.5} (1999–2001 sampling period) and PM₁₀ (1989–1996) from TEOM measurements as well as with PM_{2.5} (1999–2001) from gravimetric measurements. In single-pollutant models, mortality risk associated with a 10 µg/m³ PM increase for the different metrics ranged from 3.8% to 6.3%. Significant associations were also observed with EC, NO₃⁻, V and Ni. In two-pollutant models, the largest effect was observed in those combining traffic density with NO₃⁻ (18.0% reduction) or EC (16.6% reduction), while SO₄²⁻ values (for both the 1975–1981 and 2002 periods) showed negative effects when combined with traffic density. Three-pollutant models revealed that traffic density was the main contributor for the achievable effect, with a reduction of 18.8% in mortality when combined with EC and NO₃⁻. The authors concluded that traffic density remained a better predictor for mortality than PM_{2.5} or its constituents.

Two studies of the effects of chronic exposure to PM were conducted in Europe. A study was performed in seven French cities from 1974 to 2001 by Filleul et al. (2005), who used Cox proportional hazard models to estimate the relationship between chronic exposure to PM and total mortality. Exposure was assessed using ambient monitors that were installed very close to subjects' homes in order to reduce exposure measurement error. After excluding monitors influenced by local traffic, TSP and BS were both significantly associated with mortality (increased risks of 5% (95% CI 2–8%) and 7% (95% CI 3–10%) respectively) for increases of 10 µg/m³. (When the data from all monitors, including those influenced by traffic, were included, no significant association was observed, and all rate ratios were 1.01 or less. The authors hypothesized that the monitoring data from the traffic-influenced areas were unrepresentative of the mean exposure of the population in the entire areas, and introduced measurement error, which decreased the association with air pollution.) Higher risks were observed in subjects with less education (data not provided), in current or former smokers, and in people with occupational exposure to dust, gases and fumes. In Germany, Gehring et al. (2006) carried out a follow-up to a series of cross-sectional studies on mortality in women (aged 50–59) who lived in the North Rhine Westphalia area from January 2002 to May 2003. The authors compared a population from an industrial area highly exposed to air pollution with a reference population living in a non-industrial area. Participants' pollution exposures were defined as PM₁₀ and NO₂ concentrations at a home address, but local ambient monitoring station data were also considered for the exposure assessment. Major road proximity was measured by calculating the distance from home address to major roads with GIS technologies and Cox's proportional hazard models were used for data analysis. In the five years average scenario, an increase of 10 µg/m³ in PM₁₀ was associated with an increased risk of 19% (95% CI -1–45%) in all-cause mortality, after adjusting for SES and smoking.

14.8.1.3 Respiratory Mortality

Eight studies looked at the impact of PM on respiratory outcomes; these studies were conducted in North America (five), Europe (two) and Asia (one) and again, the investigations

were conducted under various environmental, economic and sociodemographic conditions. The health effects of PM were assessed using various PM metrics: PM_{2.5} (three studies), converted PM_{2.5} (one study), PM₁₀ (one study) and TSP (three studies). A number of these studies have already been described under Total Mortality; therefore, this section focuses more on their results, not specific study characteristics.

A cohort study conducted in Hamilton, ON, by Finkelstein et al. (2003) found a positive association between cardiopulmonary mortality and TSP. Compared with people in the most favourable category (higher income and lower particulate level), risk estimates for cardiopulmonary mortality were increased by 14% (95% CI -14–51%) for the high income–high pollution group, 81% (95% CI 12–192%) for the low income–low pollution group and 166% (95% CI 43–397) for the low income–high pollution group. As mentioned previously, this study estimated exposure using GIS at each subject's residence; a more accurate exposure representation than average air pollution measurements obtained from central ambient monitors. A cross-sectional study by Jerrett et al. (2005a) performed in Hamilton (1985–1994) showed that an increase of 10 µg/m³ TSP was significantly associated with higher cardiorespiratory mortality in both women (14% (95% CI 3–25%)) and men (17% (95% CI 12–21%)). Again, this research used modelling techniques to better reflect personal exposure. Both studies reported risk estimates several times higher than that for cardiopulmonary mortality in the ACS Study (9% (95% CI 3–16%)) for a comparable increase in PM_{2.5} (Pope et al., 2002).

Studies by Pope et al. (2004b) and Krewski et al. (2005) employed the ACS dataset to assess the respiratory mortality associated with PM during a 16-year period using Cox proportional hazard survival models. Models controlled for age, sex, race, smoking, education, marital status, BMI, alcohol consumption, occupational exposure and diet. Only single-pollutant models were used in both studies. The Pope team first established an expected pattern of PM mortality with specific causes of death based on hypothesized general pathophysiological pathways (e.g. accelerated progression of COPD). A hypothesis regarding the relationship between smoking and air pollution was also evaluated. Results revealed that respiratory mortality was not consistently associated with fine PM. Moreover, a negative statistically significant association was observed between mortality from COPD and allied conditions and exposure to fine PM (-16% (95% CI -23% to -7%)) per 10 µg/m³ PM_{2.5}. Cigarette smoking was associated with larger risk estimates for respiratory mortality than air pollutants. A statistically significant association was, however, observed between PM_{2.5} and deaths from pneumonia and influenza, but only in the group of never-smokers (20% (95% CI 2%–41%)) per 10 µg/m³ increase in PM_{2.5}.

Krewski et al. (2005) observed an association between exposure to fine PM and cardiopulmonary mortality, but not respiratory mortality. Results of the analysis revealed that an increase of 10 µg/m³ in PM_{2.5} was associated with risk estimates of 11% (95% CI 7–16%) and 0% (95% CI -11–12%) for cardiopulmonary disease mortality and respiratory disease mortality, respectively. Similar associations were observed between a 10 µg/m³ increase in PM_{2.5} and cardiopulmonary adjusted mortality for the 1979–1983 and 1999–2000 periods (6% (95% CI 2%–10%) and 8% (95% CI 2–14%), respectively); adjustment was made for age, sex, race, smoking, education, marital status, body mass, alcohol consumption, occupational exposure, and diet. Cigarette smoking was highly associated with increased risk for all-cause, cardiopulmonary and lung cancer mortality. Among gaseous pollutants analyzed (NO₂, O₃, SO₂ and CO), only SO₂ revealed a statistically significant association with respiratory mortality.

As presented in the section on total mortality, Jerrett et al. (2005b) investigated the effects of intra-urban air pollution in Los Angeles, CA, on mortality from various causes (including lung cancer mortality) using Cox proportional hazard regression models with spatial clustering at the ZIP code area in a subset of the ACS data. A 10 µg/m³ increase in PM_{2.5} adjusted for individual confounding factors (a standard set of 44 variables, including lifestyle, dietary, demographic,

occupational and educational variables), plus proximity to freeways (500 m), was associated with a risk of 17% (95% CI 5–31%) for all-cause mortality. Corresponding risk estimates were higher for certain more specific causes of death, including lung cancer (46% (95% CI -1–116%)). When PM_{2.5} was modelled with individual confounding variables and ozone (average of four highest 8-h maxima), associations were similar in magnitude, with a lung cancer mortality increase of 52% (95% CI 2–126%).

Two studies performed in Europe also found significant associations between PM and cardiopulmonary mortality. Associations between TSP and cardiopulmonary mortality were assessed by Filleul et al. (2005) in seven French cities. As mentioned previously, monitoring equipment was located very close to study subjects in areas with contrasting pollution levels. After excluding results from monitors influenced by local traffic, increases of 10 µg/m³ in TSP and BS were significantly associated with cardiopulmonary mortality (5% (95% CI 2–8%) and 7% (95% CI 3–10%), respectively). In Germany, Gehring et al. (2006) also found positive and significant associations between air pollution and cardiopulmonary mortality in adult women. Exposure to particulate pollution was defined as PM₁₀ at home address; proximity to major roads was measured by calculating the distance from home address to major roads using GIS. PM₁₀ levels from the local ambient air monitoring station were also considered for the exposure assessment. An increment of 10 µg/m³ PM₁₀ was associated with an increased risk of 42% (95% CI 8–77%) for cardiopulmonary mortality in the adjusted 1-year scenario. In the 5-year average scenario the same increase in PM₁₀ was associated with an increased risk of 52% (95% CI 9–115%) for cardiopulmonary mortality, after adjustment for SES and smoking. A statistically significant association was also found between proximity to major roads and cardiopulmonary mortality (94% (95% CI 34–177%) per 10 µg/m³ increase in PM₁₀).

A cross-sectional study was also performed in 13 major Japanese cities (Iwai et al., 2005). Results from this study were reported for SPM and were converted into fine PM data (cPM_{2.5}); therefore, the term SPM/cPM_{2.5} was used. SPM/cPM_{2.5} was correlated with several cause-specific mortality and morbidity endpoints. In bivariate analyses adjusted for smoking, SPM/cPM_{2.5} was significantly related to deaths in females from all causes (4% (95% CI 1–7%)), and from various respiratory categories, including cardiopulmonary disease (5% (95% CI 1–9%)), pneumonia (11% (95% CI 5–17%)), bronchial asthma (21% (95% CI 6–36%)), COPD (20% (95% CI 2–38%)), and lung cancer (10% (95% CI 2–18%)). There were also increases in some cardiovascular categories (IHD and hypertensive heart disease; these are presented in the next section), and cancers of the breast, uterus and ovaries.

14.8.1.4 Cardiovascular Mortality

For cardiovascular mortality a total of 13 epidemiological studies were identified for the period 2002–2006. The majority of these studies (n = 7) were performed in North America; five were conducted in Europe, while one study originated in Asia.

Many of the studies used cardiopulmonary mortality as an endpoint. As described in more detail in the previous section, positive associations were observed in several of these studies. In two Canadian studies (Finkelstein et al., 2003; Jerrett et al., 2005a), TSP was associated with cardiopulmonary mortality, even more so in subjects with low income but high exposure to air pollution. Significant increases in cardiopulmonary mortality were also associated with TSP and BS in a European study (Filleul et al., 2005). Other significant associations with cardiopulmonary mortality were reported with PM₁₀ (Gehring et al., 2006) and PM_{2.5} (Krewski et al., 2005).

Other studies have included endpoints more specific than cardiopulmonary mortality.

An important paper is the Pope et al. (2004b) study, which used the ACS dataset to assess the potential mechanisms implicated in the relationship between exposure to PM and mortality. Three pathophysiological pathway hypotheses were examined: the first scenario associated PM exposure with increased COPD diseases and mortality; the second scenario implied increased lung inflammation and accelerated atherosclerosis, which would translate into CVD and, more specifically, IHD deaths; the third scenario implied altered cardiac autonomic function, with an association with dysrhythmia and cardiac arrest. A strong association was observed between an increase of $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ and overall IHD mortality, with a risk estimate of 18% (95% CI 14–23%). Significant associations were also observed with mortality from dysrhythmia, CHF and cardiac arrest (13% (95% CI 5–21%) per $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$); the relationship remained significant after controlling for smoking. Similar effects were observed for mortality from all CVD plus diabetes for never-smokers, former smokers and current smokers, with risk estimates of 11% (95% CI 7–16%), 9% (95% CI 7–16%) and 16% (95% CI 9–23%), respectively. The association with IHD was also elevated and significant when smoking status was considered, with risk estimates of 22% (95% CI 14–29%), 15% (95% CI 7–23%) and 16% (95% CI 7–27%) in never-smokers, former smokers and current smokers, respectively. Higher risk estimates were observed for current smokers compared with the group of never-smokers; associations were observed with additional causes of death, including dysrhythmia, CHF, cardiac arrest and hypertensive diseases.

Jerrett et al. (2005b) conducted a study in Los Angeles, CA, and also found a significant association between $\text{PM}_{2.5}$ and IHD mortality, with an increased risk, adjusted for age, sex and race, of 49% (95% CI 20–85%) per $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$. Effects remained statistically significant for IHD mortality and PM, with an increased risk of 39% (95% CI 12–73%) for an increase of $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ when individual covariates (a set of 44 variables, which included lifestyle, dietary, demographic, occupational and educational variables) were adjusted for in the model. This association became non-significant, however, when all eight ecologic variables used to control for contextual neighbourhood confounding (that considered income, income inequality, education, population size, racial composition and unemployment) were additionally included in the model. A $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ adjusted for individual confounding factors, including proximity to freeways (500 m), was associated with a increased risk of 42% (95% CI 11–72%) for IHD mortality. When $\text{PM}_{2.5}$ was modelled with individual confounding variables and ozone (average of four highest 8-h maxima), associations with all-cause and IHD mortality were similar in magnitude.

As described in the previous subsections, Krewski et al. (2005) investigated the effects of air pollution on cardiovascular and cardiopulmonary mortality using data from the ACS cohort with an additional 10 years of data, including better control for workplace exposure and some dietary variables. Significant associations were found between air pollution and mortality. For the whole reanalysis period (1982–1999), an increase of $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ was associated with increased risks of 13% (95% CI 8–19%) and 11% (95% CI 7–16%), respectively, for cardiovascular and cardiopulmonary mortality. In addition, a $10 \mu\text{g}/\text{m}^3$ increase in $\text{PM}_{2.5}$ was associated with cardiopulmonary mortality risk increases of 6% (95% CI 2–10%) for the 1979–1983 period and 8% (95% CI 2–14%) for the 1999–2000 period. Sulphate (as well as cigarette smoking) also showed significant associations with cardiopulmonary mortality.

In an extended follow-up of the Harvard Six Cities Study, Laden et al. (2006) observed that a reduction in $\text{PM}_{2.5}$ levels was associated with a decrease in cardiovascular mortality; the risk estimate was -31% (95% CI -54–1%) per $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ when comparing average $\text{PM}_{2.5}$ concentrations between 1990–1998 and 1980–1985. Associations between an increase of $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$ and cardiovascular mortality were consistently significant, considering all years

(1974–1998) and the 1974–1989 period only (28% (95% CI 13–44%) and 28% (95% CI 14–43%), respectively).

Chen et al. (2005a) published results from a cohort study of subjects enrolled in the AHSMOG study (conducted in three California large metropolitan areas from 1977 to 1998) that explored the association between ambient fine PM and fatal CHD. Cohort subjects were white non-smoking adults living in California urban areas, plus a small random sample of subjects from other California areas (in order to increase pollutant variation). The current study population was restricted to nine California airport airshed areas, since fine PM data were unavailable on a state-wide basis. Subjects with CHD, stroke or diabetes at baseline were excluded from the study. Monthly air pollution estimates were interpolated to participants' ZIP code centroids for home and work location within 50 km from a monitoring station. PM_{2.5} estimates were obtained by multiple regressions of state airport daily visibility values. Information considered for analyses included smoking history, education, meat consumption, ETS, time spent outdoors, activity level and dietary habits. Information was gathered in the study baseline questionnaire as well as with four subsequent follow-up questionnaires. Associations between pollutants (PM₁₀, PM_{10-2.5}, PM_{2.5}, O₃, SO₂ and NO₂) and mortality from CHD were assessed using Cox proportional hazard regression models. In single-pollutant models statistically significant associations were observed between exposure to PM and fatal CHD after adjustment for smoking, BMI, meat consumption, and calendar time, but only in females; a 10 µg/m³ increase in PM_{2.5} was associated with increased risks of 42% (95% CI 11–81%) and 49% (95% CI 17–89%) in all females and in postmenopausal females, respectively. For PM₁₀ and fatal CHD, the same increase was associated with increased risks of 22% (95% CI 6–40%) and 30% (95% CI 8–57%) in all females and in postmenopausal females, respectively. In two-pollutant models, statistically significant associations were also observed for PM when ozone was included in the model, but only in females; for CHD mortality, a 10 µg/m³ increase in PM_{2.5} was associated with a risk increase of 100% (95% CI 51–164%) while a 10 µg/m³ increase in PM₁₀ was associated with a 45% (95% CI 31–61%) risk increase. For males, all risk estimates were non-significantly decreased in both single- and two-pollutant models. No statistically significant associations were found between gaseous pollutants and cardiovascular mortality.

In a case-control study conducted in Stockholm, Sweden, Roselund et al. (2006) investigated the association between mortality related to first MI and annual concentrations of traffic-related pollutants at each subject's residence (modelled using emissions data and dispersion models) in the Stockholm County population aged 45–70 between 1992 and 1994. A borderline significance risk estimate of 238% (95% CI 0–1056%) was reported between chronic exposure to a 10 µg/m³ increase in traffic PM₁₀ and out-of-hospital MI deaths. Risk estimates for all MI deaths and for in-hospital deaths were non-significantly increased. A positive but non-significant association was found between chronic exposure to traffic PM₁₀ and fatal MI, after adjusting for heating by inclusion of SO₂ in the model (96% (95% CI -26–411%) for a 10 µg/m³ increase in PM₁₀; the corresponding risk estimates were significantly increased for each of NO₂ and for CO. Potential effect modification was observed with higher risks among women, never-smokers, subjects with more than a high school education and non-diabetic subjects.

In Sheffield, UK, two ecological correlation studies were carried out by Maheswaran and collaborators. The first study focused on stroke-related mortality and hospitalizations in subjects aged ≥45 years between 1994 and 1999 (Maheswaran et al., 2005a). PM₁₀, NO_x and CO were modelled and interpolated to census enumeration districts. Regression models were adjusted for gender, age, socioeconomic deprivation and smoking prevalence. There was an increase in stroke mortality in the highest quintile of PM₁₀ exposure (mean 23.3 µg/m³) compared with the lowest (mean 16.0 µg/m³) with an adjusted rate ratio of 1.33 (95% CI 1.14–1.56). In models adjusted only for gender and age, PM₁₀ was significantly associated with stroke mortality and

hospitalization in the fourth and fifth quintiles. A trend of increasing mortality was observed with increasing quintile. Analyses to account for population daily movement, modelled as spatially smoothed pollutant concentrations within a 1-km radius (the average walking journey distance, according to surveys, as reported by the authors) resulted in an increased rate ratio of 1.24 (95% CI 1.05–1.47) for stroke mortality in the highest quintile for PM₁₀ relative to the lowest.

The second study investigated CHD-related mortality and hospitalization using the same modelled air pollution values and adjusted for the same parameters (Maheswaran et al., 2005b). A non-statistically significant association was observed between CHD-related mortality and exposure to PM₁₀. In the highest quintile (compared with the lowest quintile) the risk estimate was 1.08 (95% CI 0.96–1.20). Statistically significant and similar effects were observed when spatially and non-spatially smoothed models were adjusted for gender and age; however, these effects disappeared when deprivation and smoking were included.

Finally, as mentioned previously, a Japanese cross-sectional study (Iwai et al., 2005) also reported significant associations between PM air pollution and cardiovascular mortality in both males and females. Age-adjusted risk increases for mortality from hypertensive heart disease and from IHD were respectively 49% (95% CI 12–85%) and 16% (95% CI 7–26%) in males and 31% (95% CI 1–60%) and 18% (95% CI 9–26%) in females per 10 µg/m³ increase in cPM_{2.5}.

14.8.1.5 Summary and Considerations: Chronic Mortality Studies

The major effort devoted to examining relationships between chronic exposure to ambient PM air pollution and mortality has been in the reanalysis of results from several cohorts, principally the ACS and Harvard Six Cities Study cohorts. While these studies have been available since the mid-1990s, some issues related to analysis raised questions about interpretation of their results. Subsequent reanalyses have dealt with these issues and, in addition, have added a number of new insights to the overall understanding of effects. As well, several additional, though smaller, cohorts have also been analyzed.

All of the chronic mortality studies published from 2002 to 2006 and reviewed in this assessment show positive, usually significant relationships between long-term exposure to various particulate pollutant metrics (most often PM_{2.5}, but also PM₁₀, TSP, BS and SO₄²⁻) and total, cardiovascular and cardiopulmonary mortality. In contrast, when deaths due to respiratory causes were analyzed separately, there is limited and inconsistent evidence for an effect of PM on respiratory mortality. (While cardiopulmonary mortality would include deaths from respiratory causes, it is largely driven by cardiovascular mortality.) The evidence that PM is associated with mortality from lung cancer, based primarily on analyses and reanalyses of the ACS and Harvard Six Cities cohorts, as well as the AHSMOG cohort, is somewhat limited; risk estimates for lung cancer mortality are consistently increased, though most of them are not statistically significant.

Cardiac outcomes have also been better characterized in the reviewed literature; when more specific cardiovascular outcomes were examined, these were for the most part significantly increased, and as expected the risk estimates were greater in magnitude than those for the broad categories of all-cause, cardiovascular or cardiopulmonary mortality. Mortality from IHD is noteworthy in this regard, both in terms of consistency and the magnitude of the relative risk. Overall, it has become clear that the cardiovascular effects of PM underlie the majority of the air pollution-related mortalities.

One of the most important results of these analyses is that mortality is predominantly related to the fine PM size fraction, with coarse PM, NO₂ and CO showing little effect in the literature reviewed. Ozone and SO₂ are, in some cases, also significantly related to mortality, although it has been argued that SO₂ is an indicator of fine PM from specific sources. In addition, the PM-

related risk estimates are generally significant after adjustment for a wide range of other risk factors for the various causes of mortality.

While other cohorts have been analyzed, the ACS and Harvard Six Cities studies remain the most prominent and provide the most reliable risk estimates, due principally to their design (e.g. large size, based on the general population). In these and other studies, the new analyses have confirmed previous results but have also provided more precise evidence of the impact of PM on susceptible subgroups, such as those with IHD. The ACS cohort, due to its larger size and extended follow-up, is generally used in estimating risk; however, the Harvard Six Cities Study is also used, and observed even higher risk estimates than in the ACS Study. Both of these studies have been analyzed to estimate the length of life lost due to air pollutant exposure and, while there is some variation, the estimates are substantial, ranging from several months to 2 years. A few recent Canadian cohort studies, though with less statistical power due to smaller sample size and issues related to study design, also found significant mortality risks, with some results indicating that socioeconomic factors may play a role in the magnitude of the effects, with greater effects for lower socioeconomic status.

A small number of these studies, including analyses of the ACS cohort and some of the Canadian cohorts, have explored the association between PM air pollution and more precise exposure measures (e.g. ambient PM estimated at each study subject's residence). Most of these studies have found that the relative risk for the more precise exposure measure was much greater than that based on concentrations at a central monitoring station. This finding suggests that considerable exposure measurement error may result from the conventional use of central site concentrations in studies of the health effects of long-term exposure to air pollution, and that the risk estimates, which already represent substantial impacts on public health, may be several-fold greater than those estimated in most studies.

Overall, the database on mortality from chronic exposure to air pollution has been greatly enhanced since 1999, with new analyses and reanalyses of existing cohort data indicating a substantial impact of fine PM on public health. The results of the studies discussed above consistently indicate that PM pollution induces a significant effect on mortality (particularly from all non-accidental, cardiopulmonary, and various cardiovascular causes of death), and that this occurs at ambient concentrations relevant to conditions in Canada. In the studies reviewed, average PM_{2.5} ranged from 9 µg/m³ to 29 µg/m³, while mean PM₁₀ ranged from 19 µg/m³ to 43.7 µg/m³. Fine PM continues to be the dominant factor in explaining the long-term effects of air pollution on premature mortality, and thus provides a strong scientific rationale for the establishment of a long-term ambient air quality target.

14.8.2 Morbidity Studies

The acute effects of PM daily variations on lung inflammation, respiratory symptoms and lung function are generally considered to be transient and reversible. Exposures to very low levels of PM over long periods of time could result in chronic effects and would be viewed in a more serious light from the perspective of standard-setting. In contrast to the large number of studies on daily variations in pollution associated with mortality and morbidity, relatively few studies have examined the effects of long-term or chronic exposure to fine PM on various respiratory or cardiovascular health endpoints.

14.8.2.1 Summary of the 1999 PM SAD

The 1999 PM SAD reviewed seven studies evaluating the impact of chronic exposure to PM on respiratory disease. The increases in prevalence and incidence of chronic bronchitis and decreases in lung function, capacity, growth and development that were shown in children

across North America after chronic or lifetime exposure to acidity, sulphate and fine particulate pollution were considered to be true chronic effects. There were also indications from a long-term (20–25 year) cohort study of older adults that this increased incidence of respiratory disease, and probably also the reduced lung capacity that accompanies it, are carried over into adulthood as increased susceptibility to the adverse effects of air pollutants. Although the development of lung cancer was also associated with fine particulate air pollution, the associations were weak by comparison with other lifestyle factors such as smoking.

14.8.2.2 Summary of the US EPA 2004 PM AQCD

Several new epidemiological studies that investigated chronic exposure to PM on morbidity endpoints (respiratory symptoms, lung function) published since 1997 were discussed in the US EPA 2004 PM AQCD. Some studies were performed in the US and were based on data from the CHS and AHSMOG cohort studies. Numerous new European, Asian, and Australian studies were also reviewed in the document.

The EPA concluded that, in general, studies indicated that long-term exposure to PM_{2.5} was associated with reduced lung function growth and increased risk of developing chronic respiratory illness. Results from studies based on the CHS cohort of children in Southern California built upon the limited evidence available in the 1996 PM AQCD, indicating that long-term exposure to PM_{2.5} was associated with the development of chronic respiratory disease and reduced lung function growth. These new findings supported the results of an earlier cross-sectional study in 24 US and Canadian cities in which long-term PM exposure was associated with some effects on respiratory function and respiratory illness. The US EPA 2004 PM AQCD also reported the results of a study by Avol et al. (2001) of CHS teens who moved to other locations, in which those subjects who moved to communities with lower PM₁₀ showed recovery of growth in lung function and those who moved to areas with higher PM₁₀ had reduced lung function growth. These findings suggest that PM-related changes in lung function growth may be reversible, at least during the period of rapid lung growth accompanying physical development during the teen years, if PM exposures are lessened. As reported in the US EPA 1996 PM AQCD, it was concluded that it is more difficult to assess the strength of evidence from long-term exposure studies, because there are fewer studies available. As a result of still more limited evidence, the US EPA made no conclusions regarding long-term exposure to PM_{10-2.5} or UFPs in relation to morbidity endpoints.

14.8.2.3 Respiratory Outcomes

This review includes 17 studies conducted during the 2002–2006 period that investigated the effects of exposure to chronic PM on respiratory endpoints. In total, six studies were conducted in North America, eight in Europe, and three in Asia. The majority included only single-pollutant analyses; three studies included both single- and multi-pollutant models. PM₁₀ was used as the PM metric in 11 studies while PM_{2.5} was studied in 8 studies. Other PM indicators considered in some studies included BS, EC and SPM. No new Canadian studies were identified.

The CHS, initiated in 1992, was a large 10-year prospective cohort study of the effects of chronic air pollution exposures on the health of children living in Southern California. The aim of this study was to answer three questions: 1) Do children living in high air pollution areas suffer deleterious chronic respiratory effects? 2) Do children living in high air pollution areas suffer greater rates of acute respiratory illness, more severe respiratory illness and/or exacerbation of underlying disease (e.g. more asthma episodes for asthmatics)? 3) Are there subpopulations of children more susceptible to air pollution health effects than their peers? Children were chosen since they may be more affected by air pollution because their respiratory and immune systems are still developing and they can have higher exposures to air pollution than adults. About 5,500

children from 12 communities with different combinations of high and low levels of various air pollutants were enrolled in the study; two-thirds of them were enrolled as fourth-graders. In 1996, an additional 175 fourth-graders from each community were added to the cohort. Information on the children's health, their exposures to air pollution as well as many other factors that affect their responses to air pollution was collected and gathered annually until they graduated from high school. Levels of O₃, NO₂, acid vapour and both PM_{2.5} and PM₁₀ were measured continuously in each community throughout the study as well as for short periods in schools and in some homes. The lung function of each child was tested every spring. Questionnaires were administered annually to collect information on children's respiratory symptoms as well as other factors that could influence their response to air pollution (wheezing, chronic cough, diagnosis of asthma or asthma-related problems, time spent outside, level of physical activity, parental smoking habits, number of siblings, mould and pets in the household).

Four new studies were identified (McConnell et al., 2003, 2006; Gauderman et al., 2004; Millstein et al., 2004) that used data from the CHS cohort to investigate possible associations between morbidity effects and long-term exposure to particulate air pollution.

McConnell et al. (2003) investigated the relationship between bronchitic symptoms and ambient air pollution in CHS children with a history of asthma who completed two or more yearly follow-up questionnaires after 1996 (n = 475). A child was considered to have chronic bronchitic symptoms during the previous year if bronchitis was diagnosed or if daily cough for 3 months in a row or congestion or phlegm for 3 months in a row was reported in the questionnaire. Information on potential confounders was collected with the baseline questionnaire (child's sex, age, race and ethnicity, history of allergies, family history of asthma, whether the child smoked, *in utero* tobacco smoke exposure, membership in a health insurance plan and SES based on family income).

The researchers examined the associations of bronchitic symptoms with both the ambient air pollutants' yearly deviation from the 4-year mean within the 12 communities and with the 4-year average of air pollutants across the 12 communities, based on three-stage regression models. Individual time-dependent covariates (including within-community variability, age, children's smoking history, and second-hand tobacco smoke exposure) were assessed in the first stage using logistic regression; individual level time-independent confounders were assessed in the second stage with the linear regression model; in the third stage the effects of 4-year average air pollutants were estimated. To yield a more efficient logistic mixed-effects model, the three regression models were combined. Single- and multi-pollutant models were used.

Results revealed significant associations between bronchitic symptoms and PM_{2.5}, EC and NO₂ in the between-communities analysis; significant associations were also observed for PM_{2.5}, OC, NO₂ and O₃ in the within-community results. For PM_{2.5}, an increase of 10 µg/m³ within the community was associated with increased bronchitic symptoms (adjusted risk estimate: 86%, 95% CI 10–157%). A borderline significant association was found with PM₁₀ in both within- and between-communities results, with adjusted risk increases of 39% (95% CI -10–95%) and 10% (95% CI 0–20%) for an increase of 10 µg/m³, respectively. For the within-community effect, the PM_{2.5} estimate was only modestly attenuated by other pollutants and remained significant after adjustment for coarse PM (PM_{10-2.5}), inorganic and organic acid. The effect of OC remained significant except with PM_{2.5} or NO₂, while NO₂ was reduced and no longer significant with O₃ or PM_{2.5} and was markedly reduced after adjustment of OC. The between-communities estimates for PM₁₀ and PM_{2.5} were generally not significant in the presence of other pollutants. The results of this study suggest a role for chronic exposure in the exacerbation of asthma in children. The authors also concluded that NO₂ and OC deserve greater attention as potential causal agents of chronic bronchitic symptoms in asthmatic children.

In a follow-up paper McConnell et al. (2006) used the same statistical approach to examine whether the effect of air pollution on the prevalence of bronchitis in the same group of asthmatic CHS children was greater among dog and cat owners. The authors also assessed other exposures that might interact with air pollution explained by dog/cat in the home (e.g. sex and parental history for asthma). Risk estimates between bronchitic symptoms in asthmatic children owning dogs and air pollutants were positive and significant for all pollutants except PM_{10-2.5} and organic acid (these were both positive, but non-significant). The risk estimates between bronchitic symptoms and yearly variability in PM₁₀ among children owning a dog and children without a dog at home were 77% (95% CI 19–137%) and -19% (95% CI -92–54%), respectively, per 10 µg/m³ PM₁₀ (p-value for interaction of air pollution effect with dog ownership = 0.02). For PM_{2.5}, a risk increase of 131% (95% CI 41–221%) was found per 10 µg/m³ increase in children owning a dog compared with 9% (95% CI -101–117%) for children without a dog (p-value for interaction of air pollution effect with dog ownership = 0.06). Patterns were similar for each of EC and OC. A weaker and non-significant interaction was found between cat ownership and air pollutants and the association with bronchitic symptoms. The largest effects were observed in children owning both a cat and a dog (104% increased risk (95% CI 23–185%) for an increment of 10 µg/m³ in PM₁₀ and 135% (95% CI 6–265%) for an increase of 10 µg/m³ in PM_{2.5}). Even stronger effects were observed for EC and OC. Interaction between endotoxin and air pollutants was suggested as a plausible explanation for these results.

Gauderman et al. (2004) investigated the impact of chronic exposure to air pollution on various pulmonary functions, including FVC, FEV₁ and MMEF, in the CHS. Potential confounders (including height, BMI, race, presence or absence of Hispanic ethnic background, doctor-diagnosed asthma, any tobacco smoking by the child the preceding year, exposure to ETS, exercise or respiratory tract illness on the day of the test) were incorporated into the model. For girls, the average FEV₁ increased from 1988 mL at the age of 10 years to 3332 mL at the age of 18 years, and from 2082 mL to 4464 mL for boys; similar patterns of increase were also observed for FVC and MMEF. Negative relationships were observed between various air pollutants and growth in FEV₁ over the 8-year study period. Results found in this study were based on increments of 22.8 µg/m³ for PM_{2.5} and of 1.2 µg/m³ for EC. Significant associations were found between reductions in growth of FEV₁ and PM_{2.5} (OR = -79.7 mL; 95% CI -153.0 mL to -6.4 mL; p = 0.04), and EC (OR = -87.9 mL; 95% CI -146.4 mL to -29.4 mL; p = 0.007) as well as between MMEF and EC (OR = -165.5 mL; 95% CI -323.4 mL to -7.6 mL; p = 0.04). No statistical associations were found with OC. Significant associations with several pulmonary functions were also found for NO₂ and acid vapour. No significant differences were observed between genders with respect to air pollution effects on lung function growth.

All pollutants were associated with FEV₁ and FVC growth deficits; similarly, growth of MMEF was associated with all pollutants but ozone. In general, two-pollutant models did not provide a better match between air pollutants and adverse health effects than single-pollutant models. Statistically significant deficits were also observed between attained FEV₁ at the age of 18 years and various air pollutants, including NO₂ (p = 0.005), acid vapour (p = 0.01), PM_{2.5} (p = 0.002) and EC (p = 0.006). For PM_{2.5}, the estimated proportion of children with low FEV₁ (FEV₁ < 80% of predicted value) was 1.6% in the least polluted area as compared with 7.9% in the most polluted area: 4.9 times higher. This study demonstrated that exposure to current air pollution levels can produce chronic adverse effects on the lung development of children.

Millstein et al. (2004) investigated the effects of air pollution on asthma medication use and the prevalence of wheezing among children enrolled in the CHS. Air pollutants included in the analysis were PM₁₀, PM_{2.5}, PM_{10-2.5} (calculated by difference between PM₁₀ and PM_{2.5}), O₃, NO₂, HNO₃, acetic acid and formic acid. Of the 2,034 fourth-grade children, 14.5% (n = 294) had physician-diagnosed asthma and 32.3% (n = 656) had experienced some lifetime history of

wheezing. Concentrations of the various air pollutants were not reported in the paper; annual IQRs for PM₁₀, PM_{2.5} and PM_{10-2.5} were respectively 13.39 µg/m³, 5.24 µg/m³ and 11.44 µg/m³. Concentrations of PM₁₀ and PM_{10-2.5} were strongly correlated (r = 0.91), while the correlation between PM₁₀ and PM_{2.5} levels was moderate (r = 0.33). Data were stratified by season (March–August (summer) and September–February (fall/winter)). Multilevel mixed-effects models accounted for age, allergies, sex, race, home heating system, pet cats, carpets or water damage in home, education of parent/guardian completing questionnaire, ETS and physician-diagnosed asthma. Only lag 0 d was considered in the main analysis, but a sensitivity analysis considered a 14-d lag period. In the March–August period PM₁₀ was associated with a higher prevalence of wheeze (an increased risk estimate of 80% (95% CI 28–131%) for a 10 µg/m³ increase (p = 0.006)); the PM_{2.5} risk estimate was much lower (18% (95% CI -121–156%) per 10 µg/m³). No significant associations were found for any PM fraction in the fall/winter period or in the annual analysis. No association was found between asthma medication and any PM size fraction during any time period. Moreover, as the authors noted, the absence of association between PM₁₀ and wheezing in the fall could result from differences in PM composition between regions as well as from differences between seasons.

In summary, all new studies using data from the CHS cohort have observed significant associations between chronic exposures to PM and various respiratory health outcomes, including reduced lung function growth and increases in the prevalence of bronchitic symptoms such as wheezing in asthmatic children.

Another US cohort study investigated the effects of air pollution on pulmonary exacerbation (PE) and lung function, as well as mortality, among subjects 6 years and over with cystic fibrosis during 2000 (Goss et al., 2004). Models were adjusted for the following individual risk factors: weight, race, airway colonization, pancreatic function and insurance status. No data were available to control for tobacco use or exposure to ETS. Single- and multi-pollutant analyses were performed. Increases of 10 µg/m³ in PM₁₀ and PM_{2.5} were associated with increases of 8% (95% CI 2–15%) and 21% (95% CI 7–33%), respectively, in the odds of having two or more PEs. Ozone was also significantly associated with PE; weaker associations were reported in individuals who experienced two exacerbations per year or less. Particulate air pollution estimates were no longer significant when the baseline percentage of predicted FEV₁ was added into the model, while results for ozone were unaffected by this addition. A 10 µg/m³ increase in PM_{2.5} was associated with a decrease of 24 mL (95% CI 7–40) in FEV₁ in 2000 after adjustment for age, gender, height and mean FEV₁ in 1999, while an increase of 10 µg/m³ in PM₁₀ was not associated with a significant change in FEV₁ (OR = -1 mL; 95% CI -7–10 mL).

Tager et al. (2005) also investigated the impact of chronic exposure to air pollution on lung function in young adults (n = 255 never-smoking students from Los Angeles and San Francisco, CA, aged 16–19). Air pollutant (O₃, NO₂ and PM₁₀) exposure was calculated from ambient air monitors and interpolated to subjects' residences using a geocoding approach. The study mainly focused on ozone exposure, but some results were reported for PM measurements. In single-air-pollutant models, the authors reported inverse associations between forced expiratory flow after 75% of expired volume (FEF₇₅) and estimated lifetime mean 8-h exposure to PM₁₀ (decrease of 9% per 10 µg/m³) in men, and decrease of 10% per 10 µg/m³ in women). Similar relationships were also observed with O₃ and NO₂. In two-pollutant models, associations with O₃ were more robust than with PM₁₀ or NO₂; the main effect parameter estimates were substantially reduced for both PM₁₀ and NO₂.

Eight European studies (Brauer et al., 2002, 2006; Janssen et al., 2003; Karakatsani et al., 2003; Solomon et al., 2003; Penard-Morand et al., 2005; Schikowski et al., 2005; Pierse et al., 2006) investigating the impact of chronic exposure to PM on respiratory morbidity were reviewed and are summarized in the following paragraphs.

In a prospective cohort study conducted in the Netherlands, Brauer et al. (2002) examined the relation between ambient PM and the occurrence of respiratory infection, asthma and allergic symptoms in a cohort of children 2 years of age whose mothers were part of the Prevention and Incidence of Asthma and Mite Allergy Study. Average concentrations of PM_{2.5}, NO₂, and soot (measured as reflectance on the PM_{2.5} filters, closely related to EC) were calculated at each subject's birth address using ambient air pollution monitoring data and GIS variables for modelling. Adjustments were made for maternal smoking during pregnancy, smoking in home, type of study, mattress cover, parental education, sex, indoor sources, ethnicity, breastfeeding at 3 months, mould at home, pets, parental allergies, area of residence and mother's age. A multiple logistic regression analysis was carried out to evaluate the association between air pollution and health outcomes. A 10 µg/m³ PM_{2.5} was significantly associated with an adjusted estimated risk of 57% (95% CI 3–110%) for ear, nose and throat infections. A positive non-significant association with wheezing was also observed (adjusted risk increase 41% (95% CI -6–91%)). In addition, sensitivity analysis was performed to assess the impact of considering only children who had not moved in the first 2 years of life, since the investigation considered health outcomes in 2-year-old children. The analysis considered two scenarios: first by excluding children who moved between the ages of 3 months and 1 year, second by excluding children who had moved before age 2. In the first scenario, with fine PM, results revealed an increased risk for asthma, with an adjusted risk estimate of 54% for asthma (95% CI -40%–147) compared with 35% (95% CI -54–127%) in the main analysis. Soot also revealed a higher risk for asthma, with an estimated increase of 16% (95% CI -9–41%) compared with 11% (95% CI -13–36%) in the main analysis, for an IQR of 0.54 (10⁻⁵/m). In the second scenario, asthma risks were significantly reduced, with risk estimates of 6% (95% CI -98–107%) and 1% (95% CI -27–29%) respectively for the above increments of fine PM and soot; however, in this case, sample size was markedly reduced (n = 2,239 compared with n = 3,696 in the main analysis).

In a further study, Brauer et al. (2006) examined the relationship between otitis media and exposure to traffic-related air pollutants in two prospective cohorts, one in the Netherlands and the other in Munich, Germany. The Netherlands birth cohort was drawn from various communities that were included in a study aimed at asthma prevention, while the Munich birth cohort focused on factors affecting immune system development and allergy in East and West Germany. In both countries, PM_{2.5}, EC (using light-absorbing carbon measurements) and NO₂ were measured at 40 sampling sites designed to track variations in traffic-related air pollution during four 2-week periods over a year. Traffic intensity, road characteristics and population in the vicinity were also assessed for each sampling site. Cohort exposure was calculated at home addresses using GIS and air pollution values. Otitis media data were obtained from a parent-completed questionnaire covering the children's first 2 years of life. Potential confounders such as sex, maternal smoking during pregnancy, indoor moulds and dampness, as well as pets at home, were controlled for. The association between health outcomes and subjects' exposure to air pollution was assessed using multiple logistic regressions. Statistically significant results were only found in the Netherlands cohort. For otitis media an adjusted increased risk of 41% (95% CI 0–80%) was observed for an increase of 10 µg/m³ in PM_{2.5} for the 2 years of age period (cumulative). For EC, a statistically significant association was also found, with an adjusted OR of 10% (95% CI 0–20%) per 0.5 µg/m³ for the 2 years of age period (cumulative). In the German cohort, ORs became slightly larger after adjustment but remained non-statistically significant. In all cases, associations between PM_{2.5} and otitis media were slightly stronger than associations with EC.

In the Netherlands, Janssen et al. (2003) investigated the relationship between PM_{2.5} and current conjunctivitis, any history of hay fever and positive skin prick test (SPT) to outdoor allergens in schoolchildren whose school and home were located close to motorways. Air pollution measurements (PM_{2.5}, benzene and NO₂) were taken outside each school on a weekly

basis; reflectance of fine PM filters was also measured as a proxy for EC, itself a proxy for diesel soot. A $9.3 \mu\text{g}/\text{m}^3$ increase in soot (EC) was significantly associated with increased risk for current conjunctivitis (adjusted increased risk 93%, 95% CI 14–172%) and elevated total IgE (adjusted increased risk 98%, 95% CI 15–181%); fine PM was also significantly associated with current conjunctivitis (adjusted increased risk 103% (95% CI 22–185%)) per $10 \mu\text{g}/\text{m}^3$ $\text{PM}_{2.5}$. When subjects with a positive SPT to outdoor allergens were compared to subjects with a positive SPT to indoor allergens, stronger associations in the former were observed for current itchy rash (EC and $\text{PM}_{2.5}$) and current wheeze and chronic bronchitis (EC). Effects were also greater in analyses that considered only children who had lived at their current address and attended their current school for >1 year or only those who lived within 500 m of a motorway. The strongest effects were observed with truck traffic and proximity to truck traffic, not with car traffic.

In Greece, a 1991–1996 study of the occurrence of chronic respiratory disease was conducted by Karakatsani et al. (2003). This nested case-control study used data from a cohort of 400,000 healthy adults participating in the EPIC study initiated in the early 1990s. All participants recruited into the EPIC project and residing in the greater Athens area were eligible for inclusion into this study. Personal exposures to BS and NO_2 long-term residential and occupational pollution were assessed using data from 14 monitoring stations. The average annual ambient BS levels from five boroughs outside Athens were considered. A group of 168 respondents who reported COPD or other respiratory symptoms for at least 3 months per year and for at least 2 years were included as cases (case-series 1). An equal number of subjects without any respiratory disease or symptoms were selected as the control group. Participants reporting heart disease, asthma or other respiratory diseases were then excluded from the study. Among the case group, a subset of 84 individuals was identified who met clinical diagnosis criteria of COPD or respiratory symptoms based on spirometry (case-series 2). Retrospective personal exposure to air pollution for the past 5 or 20 years was assessed. A statistically significant association for chronic respiratory disease was found for the 5 most recent years of exposure, with an increased risk of 70% (95% CI 5–135%) in the case-series 2 group compared with the control group. A statistically significant association was also found using a linear trend method (per exposure quartile ($<13 \mu\text{g}/\text{m}^3$, $13\text{--}24 \mu\text{g}/\text{m}^3$, $25\text{--}34 \mu\text{g}/\text{m}^3$, and $34\text{--}79 \mu\text{g}/\text{m}^3$)) with a risk of 31% (95% CI 5–58%), also in the case-series 2 group compared with the control group. Positive but non-statistically significant associations were observed with the evaluation of personal exposure over a 20-year period.

In England, Solomon et al. (2003) found no long-term effects of BS on cardiorespiratory morbidity as measured by self-reported IHD, asthma, productive cough, wheezing and use of an asthma inhaler in British women ≥ 45 years of age who returned a postal questionnaire. Only electoral wards with at least 30 years of BS data were included, and similarly only women who had lived within 5 mi of their current residence for over 30 years were included. The average BS concentrations varied from 40 to $180 \mu\text{g}/\text{m}^3$ in the 1966–1969 period, from 14 to $79 \mu\text{g}/\text{m}^3$ in the 1978–1981 period, and from 4 to $14 \mu\text{g}/\text{m}^3$ in the 1994–1997 period. After adjustment for potential confounders (smoking, tenancy, social class, childhood hospitalization for chest problems, diabetes, and BMI), the prevalence ratio of each of the above health measures in high-PM wards versus those with lower levels of PM was 1.0 or less.

In France, Penard-Morand et al. (2005) performed a cross-sectional study of schoolchildren in six cities ($n = 4,901$), investigating the effect of long-term air pollution on asthma, allergic rhinitis and atopic dermatitis from January 1998 to December 2000. Long-term exposure was assessed using average air pollutant concentrations from 29 ambient monitoring stations extrapolated to the school address using GIS techniques. Two exposure levels were considered: “low exposure” (average annual PM_{10} of $26.9 \mu\text{g}/\text{m}^3$ (range $16.3\text{--}30.0 \mu\text{g}/\text{m}^3$)), and “high exposure”

(average annual PM₁₀ of 40.6 µg/m³ (range 30.3–48.3 µg/m³)). Data were analyzed as binary (low vs. high exposure group) or continuous using logistic regression models. Adjustments were made for age, sex, family history of allergy, passive smoking and parental education. A sensitivity analysis was conducted using data from long-term resident subjects (>8 years). Effects of gaseous pollutants (O₃, NO₂ and SO₂) were also examined. Increases in 3-year averaged PM₁₀ were associated with increased risks for exercise-induced bronchitis (EIB) and lifetime allergic rhinitis, with risk estimates of 36% (95% CI 2–70%) and 28% (95% CI 4–52%), respectively, for an increase of 10 µg/m³ in PM₁₀. Effects were also observed in two-pollutant models: the association between PM₁₀ and EIB became weaker and was no longer significant, while the association with atopic dermatitis was strengthened and became statistically significant (past-year atopic dermatitis risk estimate 49% (95% CI 7–91%) and lifetime 39% (95% CI 7–69%)). Furthermore, children attending schools with higher levels of PM₁₀ had a significantly higher prevalence of clinical outcomes than children with low PM exposure (for EIB 10.3%, p < 0.001; flexural dermatitis 13.2%, p < 0.001; atopic dermatitis during past year 14.0%, p < 0.001; lifetime allergic rhinitis 21.1%, p < 0.05; lifetime atopic dermatitis 27.0%, p < 0.05; and asthma in the past year 5.9%, p < 0.05 (no CIs reported)).

Also in Europe, Schikowski et al. (2005) conducted a cross-sectional study from 1985 to 1994 to examine the effects of air pollution on women aged 54–55 with COPD. Five Rhine-Ruhr basin cities with significant pollution burdens from industry and traffic were defined as the study area and two non-industrial small towns as the reference area. Air pollution exposure was assessed in two different ways, first by using data from monitoring stations and secondly by using the distance of the residence from major roads. Self-administered questionnaires were sent to participants to assess subjects' symptoms, diagnoses and risk factors. Potential confounders such as age, socioeconomic and smoking status, ETS exposure and heating with fossil fuels were controlled for; FEV₁ and FVC were also measured and adjusted for BMI and height. Logistic regression models were used to assess linkages between air pollution and respiratory symptoms, and multiple linear regression models were used to investigate associations with FEV₁, FVC and the FEV₁/FVC ratio. The prevalence of COPD was defined using GOLD (lung function FEV₁/FVC < 0.7) criteria, and women with asthma were excluded to prevent confounding. An increase of 10 µg/m³ PM₁₀ was associated with decreases of 7.3% (95% CI 3.6–11.0%) in FEV₁ and 5.3% (95% CI 2.6–7.9%) in FVC, and an increased risk of 41% (95% CI 4–77%) for COPD prevalence. Proximity to major roads (i.e. living closer than 100 m) was associated with an increased risk of 58% (95% CI 6–111%) for COPD prevalence. No associations were reported between PM and respiratory symptoms; however, significant effects were associated with NO₂.

In the UK, a study conducted in Leicestershire assessed the effect of PM on children's respiratory health by linking 1–5 years of cohort data with modelled exposure at the home address to primary generated PM₁₀ using road-traffic data and a dispersion model of locally generated PM₁₀ (Pierse et al., 2006). Respiratory symptom information was collected from questionnaires completed by subjects' parents in 1998 and 2001. Binomial GLMs were used for analyses, with adjustment for covariates including parental asthma, home coal heating, smoking in the household, parental education, preterm birth, breast feeding, gas cooking, presence of pets, maternal smoking and diet. Further stratified analyses included data on the use of daycare by children and exposure to ETS. Prevalence of cough without a cold appeared to have a dose-response relationship based on data from both questionnaires. An increase of 10 µg/m³ PM₁₀ was associated with cough without a cold (increased risk of 191% (95% CI 68–322%) and 445% (95% CI 278–610%) for 1998 and 2001, respectively). PM₁₀ associations with nighttime cough and current wheeze were only significant in 2001 (223% (95% CI 58–365%) and 247% (95% CI 39–457%), respectively). Similar results were also obtained when data were stratified by use of daycare, exposure to ETS or age. Authors also analyzed the incidence of symptoms in 2001

based on symptom status in 1998 (asymptomatic vs. symptomatic) and found no association between PM₁₀ and persistence of symptoms in 1998 symptomatic subjects (weak statistical power to detect).

Finally, three studies (Zhang et al., 2002; Hwang et al., 2005, 2006) were carried out in Asia. In four Chinese cities, Zhang et al. (2002) investigated the prevalence of respiratory outcomes in children during a 4-year period; positive but mostly non-statistically significant associations were found between respiratory morbidity and PM size fractions (PM_{2.5}, PM₁₀, TSP and coarse PM), though there were significant associations of at least one non-fine PM fraction with bronchitis, persistent cough and persistent phlegm. In Taiwan, results from a cross-sectional study investigating the impact of traffic-related air pollution on elementary and middle school children diagnosed with asthma indicated that PM₁₀ exposure was not positively associated with asthma in single- or multi-pollutant models (Hwang et al., 2005). In a later Taiwanese study no association between PM₁₀ and allergic rhinitis in schoolchildren was observed in single- and two-pollutant models; however, significant associations with traffic-related pollutants (NO_x, CO and SO₂) were reported (Hwang et al., 2006).

14.8.2.4 Cardiovascular Outcomes

Only four new studies investigated the impact of chronic PM exposure on cardiovascular endpoints during the 2002–2006 review period; one study was carried out in the US (Kunzli et al., 2005) and the three others in Europe (Solomon et al., 2003; Maheswaran et al., 2005a, 2005b). No Canadian studies were identified.

An important US chronic cardiovascular morbidity study provided insight into the potential effect of PM_{2.5} long-term exposure on the development of CVDs. This cross-sectional study (Kunzli et al., 2005) explored the association between ambient fine PM and carotid artery intimal medial thickness (CIMT), a recognized quantitative measure of atherosclerosis. Study participants were residents of Los Angeles, CA (>40 years old) with indications of higher risk for CVD. GIS and geostatistics were used to estimate chronic PM_{2.5} levels at each participant's residence. Linear regression analyses were performed to test the association between CIMT and fine PM. Adjustment was made for confounders (age, male sex, low education and low income). After adjustment, the risk increase for an increase of 10 µg/m³ PM_{2.5} was 4.2% (95% CI -0.2–8.9%) in the whole population and 13.8% (95% CI 4.0–24.5%) for women >60 years of age. Age was the only covariate that significantly modified the CIMT point estimate, with a percentage risk reduction from 5.9% (95% CI 1.0–10.9%) to 4.3% (95% CI 0.4–9.0%). A positive but non-significant association between CIMT and ozone was observed; moreover, inclusion of ozone had no impact on the PM_{2.5} coefficient. This well-conducted study provides the first evidence that chronic exposure to fine PM may lead to effects on the CIMT, a biomarker of cardiovascular disease, in a “real world” setting. This important finding bridges the gap that existed between the epidemiology studies of long-term exposure to PM and cardiovascular mortality and the indicators of cardiovascular effects in toxicological studies in animals and humans.

As described in the previous section, an English cross-sectional survey in 11 electoral wards revealed no positive associations between living in areas with elevated BS pollution (as measured by ambient monitors) and the prevalence of cardiorespiratory morbidity, including self-reported IHD in women aged 45 years and older compared to those living in wards with lower pollution levels (Solomon et al., 2003).

The two remaining European studies were small-level ecological studies conducted in Sheffield, UK. In the first study Maheswaran et al. (2005a) found a positive association between PM₁₀ and stroke-related hospitalization during 1984 to 1999: a rate ratio of 1.13 (95% CI 0.99–1.29) was reported for PM₁₀ in the highest exposure quintile (mean 23.3 µg/m³) compared with the lowest quintile (mean 16.0 µg/m³) after adjustment for age, sex, SES and smoking. The same group

also investigated CHD using the same database (Maheswaran et al., 2005b). No association was found between PM₁₀ and CHD-related hospitalizations in the highest exposure quintile relative to the lowest quintile after adjusting for the same confounders as the earlier study (rate ratio 1.01 (95% CI 0.90–1.14)).

14.8.2.5 Summary and Considerations: Chronic Morbidity Studies

This review of studies of chronic morbidity associated with PM exposure published from 2002 to 2006 provides strong evidence of an association between particulate air pollutants and cardiovascular and respiratory outcomes. All studies performed in North America and Europe except one reported positive results between fine PM and both cardiovascular and respiratory adverse effects; moreover, most results were statistically significant. The one study that did not report positive associations revealed no consistent associations between residence in areas of elevated BS pollution and cardiorespiratory morbidity compared to residence in English wards with lower BS levels. Study weaknesses reported by the authors included a low participant response rate to the questionnaire, use of a self-administered questionnaire with no confirmed diagnosis, and a scarcity of air pollution data, which prevented analysis using other PM metrics. The long-term duration of this study could also have produced exposure misclassification; as BS releases related to coal use were significantly reduced, other sources of particulate pollution (such as major roads) could have influenced both the high and low BS-designated areas. Three other studies conducted in Asia, investigating the relationship between PM and childhood asthma, allergic rhinitis or respiratory symptoms, also revealed no associations with PM.

Studies that observed positive associations between PM exposure and chronic morbidity were performed using various methodological approaches such as cross-sectional, prospective or retrospective cohort designs. Moreover, ambient concentrations of PM studies reporting significant associations, while sometimes relatively high, were often similar to those in Canada. Across these studies annual mean PM_{2.5} values ranged from 13.4 µg/m³ to 20.3 µg/m³, while mean PM₁₀ levels ranged from 17.4 µg/m³ to 48.0 µg/m³. Other metrics of PM were also used in these studies, including SPM, BS and TSP.

Recent findings from the CHS add support to previous conclusions that chronic exposure to fine PM is associated with decreased lung function growth and increased incidence of respiratory symptoms in children. Results from the cystic fibrosis cohort also provide additional evidence for associations with PEs in a subpopulation that is likely more susceptible to the effects of air pollution.

Again, it is interesting to note that several researchers who improved PM exposure measurements by using either ambient air monitors located close to study subjects (Filleul et al., 2005) or GIS technologies (Brauer et al., 2002, 2006; Finkelstein et al., 2003; Jerrett et al., 2005a, 2005b; Penard-Morand et al., 2005; Kunzli et al., 2005; Gehring et al., 2006) found significant associations between PM and various health outcomes. In contrast, one study that did not observe significant associations (Solomon et al., 2003) relied only on data from central site monitoring. Even if some other explanatory factors could be identified, such results suggest that central air monitoring values do not fully reveal the health risks associated with fine PM exposure.

New findings from long-term studies support previous conclusions that chronic exposure to fine particles is associated with respiratory morbidity. Increasingly, studies have revealed the cardiovascular effects of long-term exposure to PM, including consistent associations with a range of specific outcomes. Most notable among the new literature was a study in which CIMT, a recognized quantitative measure of atherosclerosis, was associated with fine ambient PM, providing clear evidence linking adverse cardiovascular outcomes that have been associated

with chronic exposure to fine PM to more subtle effects on the cardiovascular system observed in panel studies and experimental settings.

14.9 Risk Characterization

14.9.1 Introduction

Risk characterization serves an integrative function in an assessment. That is, the risk characterization seeks to integrate the scientific information provided on the nature and concentrations of the “hazard” to which receptors are exposed (in this case, the pollutant fine PM, or PM_{2.5}), the nature of the effects induced by exposure to the hazard (PM-related effects reported in epidemiological studies and in toxicological studies in humans and laboratory mammals), and the quantitative relationship(s) between exposure of receptors and the responses they exhibit (i.e. the concentration–response relationships). Together, this information is used to estimate the magnitude of impacts expected under current (and future) exposure conditions.

This section presents the first part of such an analysis. Summaries of the key information on exposure and effects of PM_{2.5} (and some other PM metrics) described in detail in sections 14.1 to 14.8 are presented here. The summary information is then presented in an integrated fashion and the weight of evidence is evaluated to assess whether the findings support a causal association between exposure to PM_{2.5} and various categories of health effects. The shape of the concentration–response curve and the populations that are most at risk from exposure to PM_{2.5} by virtue of having enhanced exposure and/or susceptibility are also described. Uncertainties in the data and the implications of these uncertainties are discussed. Finally, conclusions with respect to key findings and insights from the preceding subsections of the risk characterization are presented.

Quantitative assessments of the relationships between ambient PM and adverse health effects can be developed and presented separately using Health Canada’s Air Quality Benefits Assessment Tool (AQBAT). These quantitative relationships are based on an analysis of the literature that provides the most appropriate results for this purpose, and utilizes the results of both single studies and meta-analyses of multiple studies. AQBAT has been and is used to estimate the benefits of air quality risk management in federal Regulatory Impact Assessments and in establishing the potential benefits in air risk management scenario development. AQBAT includes endpoints for which strong evidence of a relationship between exposure and effect has been established. This spreadsheet tool is available upon request to air@hc-sc.gc.ca.

The database of health-related literature on PM has been developed over a long period of time but has exponentially grown in richness and complexity over the last 10–15 years. Epidemiological studies provided the initial indications of significant and widespread effects of PM and continue to provide the primary evidence of population-level impacts in studies conducted across North America and around the world, at both high and low ambient concentrations. However, toxicological studies, especially those utilizing animal models of human disease, have provided evidence for a wide array of possible mechanisms via which PM could exert effects on the respiratory and cardiovascular systems. Some evidence of other systemic effects is also emerging.

14.9.2 Summary of Exposure and Effects

14.9.2.1 Exposure Summary

Most epidemiological studies of the health effects of ambient PM use 24-h average PM concentrations determined at central monitoring sites as a surrogate measure of exposure.

However, the use of such monitors to reflect population exposure has regularly come into question for a variety of reasons. For example, ambient PM exhibits significant spatial heterogeneity, and monitoring stations are often at a substantial distance from individuals and populations. As well, during the course of a day, most individuals move through a variety of microenvironments and engage in diverse activities, some of which may have different sources and/or concentrations of PM than those impacting on fixed site monitors. As a consequence, population and individual exposures to PM can deviate from the concentrations measured at a central location. An understanding of human exposure to ambient PM informs the interpretation of the results of epidemiological studies of the association between ambient PM concentrations and health effects.

Ambient PM levels vary widely in Canada, though all areas can experience both large-scale regional events and localized peak events resulting from point-source emissions (see Section 14.1.4). The highest levels in Canada are found in southern Ontario and Quebec. This area is part of a larger regional airshed that encompasses northeastern North America and has influence over areas of the southern Maritime Provinces. Western parts of the country can experience some regional and peak events, often associated with forest fires and burning. Although the summer season exhibits the highest levels for most parts of the country (both for peaks and average concentrations), high pollution episodes can occur at any time of year.

As detailed in Section 14.1.5, a number of studies have investigated personal exposures to PM, including the relationship between these exposures and the concentrations measured at central ambient monitoring sites. In most of these studies, personal exposures of healthy adults and children to PM_{2.5} or PM₁₀ generally exceeded the indoor concentrations at their residences, which in turn exceeded or were similar to those outdoors. Personal exposures to PM generally had a skewed distribution and were more variable than ambient levels. The increase in the personal exposures over the indoor/outdoor concentrations has been attributed to a “personal cloud” around individuals, created by the generation and resuspension of PM through activities such as cleaning, cooking or smoking. There is also some suggestion in the available studies that the personal exposures of healthy elderly people and of children and adults with pre-existing disease conditions were not increased over indoor and outdoor concentrations (and indeed, were sometimes lower than the latter). This may have occurred because these subjects have reduced activity levels and in some instances live in settings (institutions, multi-unit housing) with mechanical filtration systems.

Correlations between ambient central site concentrations of PM and personal PM exposures have been examined in a number of studies (Section 14.1.3). In pooled studies, in which data are collected for different subjects on different days, the daily personal exposures to PM_{2.5} are generally not well correlated with the corresponding ambient fine PM concentrations. However, in longitudinal studies, where data are collected on multiple days for each subject, daily total PM_{2.5} personal exposures and ambient PM_{2.5} concentrations are strongly correlated for most, though not all, subjects. Results also indicate that the daily average of personal PM among subjects is highly correlated with PM levels from ambient monitors—an important observation for population-based time-series studies in which ambient levels are used as an indicator of population-average personal exposure and then related to the number of adverse events among the population. These types of studies also provide evidence that exposure measurement error resulting from the use of fixed ambient monitors likely has the effect of reducing the apparent magnitude of the risk estimate relative to its true magnitude.

The total personal exposure to PM that people experience in indoor and outdoor microenvironments (see Section 14.1.7) can be classified into PM of ambient origin (includes exposure to ambient PM while outside and exposure while indoors to ambient PM that has infiltrated indoors) and PM from all other sources (or PM of non-ambient origin, i.e. that

generated from indoor sources, indoor reactions, or personal activities). The size of personal exposure to PM of ambient origin relative to non-ambient PM depends on the ambient concentration, the infiltration rate of outdoor PM into indoor microenvironments, and the amount of PM generated by indoor sources and personal activities. Infiltration rates depend on air exchange rates, particle-size-dependent penetration into buildings, and particle-size-dependent removal rates. All these factors vary over time (for example, air exchange increases with the opening of windows and doors and the operation of window or attic fans, and as the indoor/outdoor temperature increases), and across subjects and building types.

A small number of studies have estimated the components of personal exposure to fine PM (as PM_{2.5} or sulphate) that are of ambient and non-ambient origin (Section 14.1.7). The results of these studies have shown that fine PM concentrations measured at central monitoring sites were strongly correlated with personal exposures to fine PM of ambient origin, but only weakly correlated with total fine PM exposures. The estimated personal exposures to fine PM of non-ambient origin were essentially uncorrelated with central site concentrations and were highly variable, due to differences in indoor sources and personal activities among the study subjects.

The strong relationship between central site and personal exposures to fine ambient PM is consistent with what is known of its environmental behaviour. In general, there is a fair degree of spatial homogeneity in ambient concentrations of PM_{2.5} within a metropolitan area, as a result of the diffuse nature of precursor sources, as well as the widespread formation and long lifetime of the high regional background of secondarily formed PM_{2.5}. In addition, most people spend the large majority of their time each day in indoor microenvironments, and it is clear that PM_{2.5} penetrates indoors more readily and deposits to indoor surfaces to a lesser extent than other size fractions of PM. As a result, a larger fraction of PM_{2.5} of ambient origin is found indoors, and the proportion of ambient PM to which people are exposed is higher for PM_{2.5}.

Overall, these findings suggest that central site ambient PM_{2.5} concentrations are a useful measure of exposure to PM_{2.5} that originates from ambient sources. In addition, since the ambient and non-ambient components of personal exposure to fine PM appear to be independent, the non-ambient exposure to fine PM is not expected to be a confounder to the effects estimate for ambient PM in observational epidemiological studies.

These conclusions are less applicable to other size fractions of PM, because ambient central site concentrations appear to be poorer measures of personal exposure to PM_{10-2.5} and UFPs, since these size fractions are more spatially heterogeneous than PM_{2.5} across urban geographic scales. In addition, these size fractions penetrate indoors less readily and deposit on indoor surfaces at higher rates compared with PM_{2.5}. Insufficient work has been conducted to date on PM components to allow conclusions to be drawn. It is evident that there is considerable variability from component to component in terms of the contribution of ambient to personal exposure, though ongoing research should begin to provide insights on this matter.

14.9.2.2 Summary of Effects in Laboratory Animals

The PM toxicology database has grown substantially in recent years. Most of this research has focused on the pulmonary and cardiovascular systems, although there are now indications that other systems such as the CNS may be important targets and/or mediators of effects. While earlier experimental animal studies focused on establishing dose–response relationships, newer studies have been designed to tease out the finer details in exploring the parameters that influence PM toxicity, specifically by comparing sources, location, and season, and by determining the PM constituents that are most important in eliciting health effects. An increasing number of studies have sought to replicate and test the complex particle mix in ambient air, either with resuspended ambient PM or through the use of particle concentrators that generate CAPs from specific locations in real time. Given the considerable uncertainties involved in

extrapolating data from animals to humans, due to differences in dosimetry, target sensitivity, metabolism and lifespan (among other disparities), animal toxicology studies primarily contribute to understanding the biological basis of particle effects and mechanisms of action.

The cardiovascular system has emerged as a critical target of PM toxicity, and much recent toxicologic research has focused on discerning the mechanisms behind the cardiovascular responses to PM. Altered vasoactivity is emerging as an important pathway (see Section 14.3.2.3) through which PM may exert these effects. Vasoconstriction, upregulation of the endothelin system, and/or impairment of vessel dilation have been reported in animals following exposure to CAPs, urban PM_{2.5} or ROFA by inhalation or instillation, and these effects have been observed under both acute and chronic exposure durations. Although the overall database is still evolving and is not entirely consistent, it provides substantial support for vasoconstriction being a key mechanism in the cardiovascular toxicity of PM. Another proposed mechanism for explaining cardiovascular responses to PM is its ability to alter blood coagulability and generate thrombosis. There is fairly consistent support from animal models for the concept of a particle-induced and inflammation-mediated prothrombotic state. Platelet accumulation, elevated plasma fibrinogen, enhanced thrombus formation and related effects have been associated with particle exposure in rodents. However there are inconsistencies in the toxicological database, including some negative findings and questions of relevance regarding particle type and exposure route in several studies.

PM has been hypothesized to impact the progression of atherosclerosis, and there is limited but evocative evidence (see Section 14.3.2.1) that subchronic exposure to environmentally relevant levels of CAPs can potentiate the progression of aortic plaques in mice prone to developing atherosclerotic lesions. Of particular note is a study in which a detrimental interaction was found between particle exposure and high-fat diet in increasing the severity of atherosclerosis in ApoE^{-/-} mice. Cardiovascular tissue damage and inflammation due to particle exposure have been observed in only a small number of studies with laboratory animals, precluding conclusions on dose-response relationships and the particle types that may be most important for these effects.

A subject of debate has been the extent to which particles exert direct effects on cardiac function, through the stimulation of nerve receptors or following transport to the heart, to affect the cardiac muscle or vasculature. Many experimental studies with compromised animal models have reported that pulmonary exposure to PM can induce ECG waveform abnormalities, alter heart rate and heart rate variability and increase the frequency of arrhythmia, although not all studies have shown consistent changes (Section 14.3.2.4). These variable results are at least in part due to the variety of animal models used, the use of artificial particles, and the use of CAPs (the composition of which can vary widely in time and space). Overall, the toxicology database suggests that PM can exert direct effects on cardiac function, but the mechanism(s) involved and the significance of these effects are not entirely clear.

Probably the best understood of PM's effects and mechanisms relate to the pulmonary system, as particle-induced lung injury is relatively well-characterized in experimental animals (see Section 14.3.3). Pulmonary exposure to PM elicits a host of interrelated histological and cellular disturbances, including increased cellularity and inflammation in the respiratory tract, elevated protein content and LDH activity in BALF, and morphological changes such as epithelial hyperplasia and fibrosis; these latter effects were especially important with longer-term exposures. Such effects have been observed with PM exposure concentrations in the range of ~0.1–1 mg/m³. The growing mechanistic evidence base points to a molecular chain reaction involving phosphorylation-dependent cell signalling and activation of the ERK/MAPK kinase pathway and NF-κB regulatory cascade. These pathways mediate the induction of cytokines such as TNF-α, MIP-2, MCP-1 and various interleukins, leading to the migration of neutrophils,

macrophages and lymphocytes to the lung and the immunomodulatory and inflammatory responses associated with particle exposure. Research has linked lung injury and inflammation with some specific PM types, such as complex combustion-related particulate materials and metals, whereas sulphuric acid aerosols, acid-coated carbon, and sulphate salts appear to cause little lung injury or inflammation, even at high concentrations. Studies with CAPs and resuspended ambient PM suggest that particle toxicity can vary by day, location and season, related to specific particle constituent concentrations. Combustion-generated particles and those from ambient environments associated with vehicles and industry tend to be more toxic than “simpler” particles, possibly due to the EC/OC, organics, metals and/or trace elements they contain. Comparative studies generally support the notion that toxicity increases as particle size decreases and particle surface area expands.

Ventilatory effects of particle exposure in animal models include decreased pulmonary functional status, altered particle clearance from the lungs, and changes consistent with airflow obstruction and bronchial hypersensitivity. Research has generally moved away from measures of pulmonary function to more sensitive histopathological and molecular endpoints, although airway reactivity in response to PM continues to be investigated (see Section 14.3.5). Studies with urban PM_{2.5}, CAPs and ROFA generally support the notion that metals may be important in AHR induction, and that its underlying mechanisms are at least partly divergent from those involved in the inflammatory effects of PM; however, the database on this endpoint is limited.

There is fairly good coherence between *in vivo* research and the proliferating *in vitro* database on PM-induced inflammation and cell damage (sections 14.3.3.1 and 14.3.3.2). Ambient urban particles, often consisting of complex chemical mixtures, have been found to be more toxic than simple artificial particles such as CB and TiO₂. Transition metals linked to cellular injury include Fe, V, Zn, Cu and Ni, although the roles of individual metals in the overall toxicity of ambient PM can be difficult to interpret due to evidence of interactions between them. Iron is commonly correlated with the bioreactivity of PM *in vitro*, which may be linked to its ability to promote the formation of ROS. Some *in vitro* research has shown that the toxicity of ambient PM can vary by season, but generalizations are not easily made across studies. While *in vitro* studies confirm that smaller-sized particle fractions are linked to higher levels of redox activity and apoptosis, some also suggest that coarse particles and PM₁₀ are associated with higher levels of cytokine production, possibly due to their endotoxin content. *In vitro* research provides mechanistic support for the hypothesis that particles invoke an immune/inflammatory cascade involving activation of cell signalling pathways and transcription factors and the expression of chemokines and other cytokines.

The induction of oxidative stress appears to be a critical mediator underlying the toxicity of many particle types, a hypothesis supported by growing evidence from both experimental animal studies and *in vitro* models (see Section 14.3.3.3). Numerous *in vivo* studies report that markers of oxidative stress are associated with tissue damage resulting from pulmonary exposure to PM, and that treatment with antioxidants prior to exposure reduces or inhibits the inflammatory response in many cases. *In vitro* models provide substantial support for a role for ROS and reactive nitrogen species in mediating particle-induced cell activation and damage.

Experimental animal research, as discussed in Section 14.3.7, is beginning to provide indications that exposure to PM may elicit a general systemic toxicity that triggers responses outside of the cardiopulmonary system. Most importantly, there are indications that pulmonary exposure to PM may lead to effects in the CNS. Recently observed neuropathologic effects in rodent studies include reduced dopaminergic neuron density, changes in neurotransmitter levels, and inflammatory and stress protein responses in the brain following pulmonary exposure to CAPs or ultrafine CB. It is not known whether these effects are the direct result of inhaled particles distributing to the brain, or whether they may arise via indirect pathways.

Compromised animal models have been developed to study how host susceptibilities alter the response to air pollution in comparison with “normal” or healthy animals. Researchers have examined the relationship between PM exposure and various susceptibility factors, especially in the use of models examining the interaction of PM with allergic responses and the pulmonary response to pathogens, and in models of compromising cardiovascular conditions such as hypertension, hypercholesterolemia and predisposition to atherosclerosis (see sections 14.3.2.1 and 14.3.6). Of the compromised animal models that have been developed, the most notable are SH rats and ApoE^{-/-} mice. The SH rat, genetically predisposed to exhibit greater oxidative stress and adverse cardiovascular responses compared with its normal counterparts, has been used as a model for human hypertension because of similarities in the process and character of disease development. Research with these rats suggests that hypertension increases susceptibility to the inflammatory and cardiovascular effects of particles, but many of these studies did not employ healthy rats for comparison. ApoE^{-/-} mice are a murine model of advanced aortic plaque used to study atherosclerosis. The majority of these studies used normal healthy animals for comparison to demonstrate that the hypercholesterolemia and predisposition towards atherosclerosis exhibited by ApoE^{-/-} mice increased their susceptibility to the cardiovascular toxicity of PM. Accelerated atherosclerosis, vascular inflammation and perturbations of heart rate and HRV have been observed in ApoE^{-/-} mice at environmentally relevant concentrations.

It has been hypothesized that exposure to ambient PM can exacerbate allergic asthma (Section 14.3.4). Experimental allergy models show that PM may affect allergic responses by acting as an adjuvant. A substantial amount of research has been carried out using rodents administered antigens such as OVA and LPS and exposed to PM, including environmentally relevant particles such as CAPs and ambient urban PM. These data support the concept that co-exposure to PM and antigen in sensitized animals aggravates airway inflammation and specific immune responses (e.g. in increasing immunoglobulin production) compared with effects caused by either particles or antigen alone. In general, smaller-sized particles appear better able to aggravate antigen-related inflammatory and immune responses than larger particles.

As discussed in Section 14.3.6.1, PM may reduce antimicrobial defence capacity. Though there are some inconsistent results in the database, many studies that looked at the interaction between inhaled or instilled PM and pathogens have observed increased susceptibility to microbial infection in animals. This heightened susceptibility may arise from inflammation or from the alteration of mucociliary clearance leading to increased pulmonary bacterial burden. Such effects have been observed under both acute and chronic exposure durations. A limited amount of research has explored genetic susceptibility factors and indicates that there are strain-specific responses to PM, including differences in AHR, inflammation, alveolar macrophage phagocytosis and mortality. This in turn provides a plausible basis for the wide range of responses to PM seen between individual humans and animals.

Another factor that may influence susceptibility to PM is age, and while not extensive the available research suggests that aged animals may be more susceptible to PM-induced effects on the lung and heart. A limited amount of research on developmental and reproductive endpoints is suggestive of effects on lung growth in neonates and differential sensitivity of neonatal airways to inhaled PM; however, these studies employed metal particles or fly ash that may not be directly relevant to the ambient environment.

As outlined in Section 14.3.8, PM has been shown to be carcinogenic in rats, but only with long-term exposure to high concentrations of non-ambient particles. Numerous *in vivo* genotoxicity studies have demonstrated the DNA-damaging abilities of ambient PM and combustion products, supporting the biological plausibility of a link between long-term exposure to particles and lung cancer.

In contrast to the relatively limited *in vivo* work in this area, a proliferating *in vitro* database (see Section 14.3.8) is shedding light on the mutagenic potential of various types of particles, in comparing PM from different sources, locations and seasons and exploring potential mechanisms. Mutagenicity has been found to reside in multiple PM chemical components, including the PAHs and semiquinones of the organic fraction and the transition metals of the polar and water-soluble fractions. In general, smaller particles are more mutagenic than larger ones, winter PM samples are more mutagenic than those of other seasons, and PM from urban areas is more mutagenic than artificial particles like CB or PM from sites not impacted by traffic or industry.

As presented in Section 14.2, there are limitations in the ability to extrapolate findings in experimental animals to humans, in large part due to differences in the structure and physiology of the respiratory systems. However, there has been extensive work characterizing these differences, and there are important insights to be gained through this type of work.

Significant work has been conducted to characterize the deposition of particles in the human and experimental animal lung in order to understand the differences and aid in the interpretation of animal studies in relation to human disease (Section 14.2.7). Findings indicate that while there are many similarities in deposition patterns, the nasal filtering properties inherent in the most commonly used animal models result in greater extra-thoracic deposition of particles in animals, versus greater thoracic and alveolar deposition in humans. In consequence, humans receive a greater dose to the respiratory surfaces of the lung for the same exposure concentration. While this complicates the interpretation of animal toxicology, it does indicate that analogous effects in humans would occur at lower external concentrations.

As described in Section 14.2.4, the extent and site of deposition varies as a result of the influence of numerous biological factors (gender, age, health status). Women exhibit slightly but significantly higher particle deposition in some areas of the lung for some particle sizes (UFPs and coarse PM). However, the absolute particle deposition is greater in men, since men exhibit a greater ventilation rate. Physical activity is a significant modifier of deposition, since it results in a shift from nasal to oral breathing, resulting in a 3- to 4-fold increase in particle deposition and an increased fractional deposition of coarse particles in the TB and alveolar regions. Because of the smaller anatomical structure of their respiratory tract and higher ventilation rate, children show a greater particle dose deposited per lung surface area than adults and a greater particle deposition in the ET and TB regions. The age difference in particle deposition may also exist for the elderly, but there are very few data for this age group. In individuals suffering from respiratory diseases, increased total lung particle deposition is associated with obstructive pulmonary disease. The uneven airflow distribution in the respiratory tract observed in individuals with pulmonary disease, and the resulting concentrated particle deposition in specific sites of the respiratory tract, representing areas of intense ventilation, could explain this association. Even in healthy individuals, modelling demonstrates areas of intense particle deposition, mainly at airway bifurcations at carinal sites. These deposition hotspots often match up with target sites of deleterious effects due to particles.

14.9.2.3 Summary of Effects in Controlled Human Exposure Studies

At the time of the 1999 PM SAD the limited dataset available from controlled exposures of humans to PM provided few insights into the observations made in epidemiological studies, and little evidence of specific health effects. These results were at least partially the consequence of the design of these types of studies, which are limited, for practical and ethical reasons, to the examination of short-term, relatively mild and transient effects in small groups of relatively healthy individuals. Subsequently a growing number of controlled human exposure studies of

the health effects of PM air pollution have used more relevant particles and CAPs drawn from various airsheds by means of particle concentrators.

With respect to respiratory effects (see Section 14.4.3), some, though not all, controlled human exposure studies have found indications of mild pulmonary or nasal inflammation (e.g. increased neutrophils in BAL) and small reductions in oxygen saturation in healthy human adults exposed for 2 h to fine CAP concentrations of from 23 to about 300 $\mu\text{g}/\text{m}^3$, usually in conjunction with intermittent exercise. There were also small CAPs-related reductions in lung function in a small number of these studies, whereas none of the studies reported significant increases in respiratory symptoms. Effects were similar or less pronounced in asthmatics, and less pronounced in COPD patients.

Cardiovascular endpoints (Section 14.4.5) were also evaluated in the majority of the available controlled human exposure studies. In most, though not all studies, inhalation of fine CAPs produced increases in blood fibrinogen suggestive of increased risk for prothrombotic effects. There was little evidence of CAP-related effects on other biomarkers that may be linked to cardiovascular outcomes, including inflammatory mediators, coagulation factors, or blood cell counts. With respect to cardiac function, decreased HRV was reported in elderly subjects exposed to CAPs in two controlled studies, but not in young subjects in an earlier study, consistent with other evidence that the elderly may be more susceptible to the effects of PM. There are also individual reports that CAPs increased ectopic beats and that CAPs-plus-ozone caused constriction of the brachial artery. Effects on heart rate, blood pressure and cardiovascular symptoms have been reported, but not consistently observed. Biomarker studies have employed a wide variety of experimental models and particle sources. More work in this area is needed to further elucidate mechanisms that may be involved in adverse effects.

A small number of recent controlled human exposure studies have investigated the health effects of UFPs, a size fraction not increased by the early particle concentrators. However, the lab-generated UFPs used in these studies originate from an artificial source (i.e. electric spark discharge between graphite anodes) and are not subject to important phenomena (e.g. aging in complex pollutant mixtures under photoreactive conditions). Therefore, like most artificial particle types, these EC UFPs are considered less relevant than CAPs.

Overall, while the database is limited and not entirely consistent, there is now some evidence from human experimental studies of respiratory and cardiac effects that provides some support for the epidemiological findings. Additional work with continued focus on ambient relevant particles and specific cardiac and respiratory endpoints is necessary to more fully characterize this area of research.

14.9.2.4 Summary of Effects in Epidemiological Studies

14.9.2.4.1 Acute exposure mortality

Many recent studies provide support for earlier causative conclusions reached on acute exposure mortality, and additionally have contributed to our understanding of some of the specific aspects of this mortality (Section 14.5.1). A majority of these studies have reported positive findings, most of which were statistically significant. The increase in risk for total mortality was in the range of approximately 0.1–3% per 10 $\mu\text{g}/\text{m}^3$ PM_{10} in most North American general population studies and was generally greater for $\text{PM}_{2.5}$ (0.7–5.6%). PM-associated increases were generally similar or greater for the same increment in those general population studies that investigated categories of mortality, particularly respiratory mortality (0.07–0.9% for PM_{10} and 1.8–7.5% for $\text{PM}_{2.5}$) and cardiovascular mortality (0.3–3.6% for PM_{10} and 0.6–11.4% for $\text{PM}_{2.5}$). For most of the studies that examined the impact of adjusting for the impact of co-

pollutants, the risk estimates for PM were fairly robust, remaining positive and most often statistically significant.

A significant feature of the newer studies is the examination of specific categories of respiratory or cardiovascular mortality, such as pneumonia, stroke, MI, COPD, IHD or CHD (see sections 14.5.1.3 and 14.5.1.4). Of note, these studies find some apparently highly sensitive groups within the population, such as the elderly in general and those with diabetes and cardiac and COPD complications in particular. In a number of studies that found positive but non-significant associations between PM and total mortality, the relationship became significant (sometimes greatly so) when the focus was narrowed to specific respiratory or cardiac outcomes. A limited dataset provides evidence of acute exposure effects on a range of other specific endpoints (e.g. dyspnea, angina) although the number of studies is currently quite small for individual outcomes. With respect to age, several studies have found associations between acute exposure to air pollution (PM_{2.5}, PM₁₀ and BS) and all-cause, respiratory or cardiovascular mortality in older adults. These results appear to implicate those older than 45–55 years of age (the point when mortality rates start to increase generally) as being most sensitive.

Other general lines of research include the influence of gender, geography and season. Females have been found to be more sensitive to PM-related mortality in a few studies, but overall results provide conflicting evidence and no general conclusion can be reached at this time. Geographic variation in response has been examined in multi-city studies for Canada, the US and Europe and indicates a fair degree of heterogeneity in results. Such results remain to be explained; however, issues of relevance include heterogeneity of PM constituents and the overall pollution mix (as well as sources), variance in socioeconomic factors, and differential prevalence of air conditioning.

Only a small number of Canadian mortality studies have been conducted in recent years. While positive and significant mortality effects were found for various PM metrics, there was also sensitivity to the inclusion of co-pollutants, with the PM association being reduced in some results. While most studies were of a single city with resultant limitations on study power, a multi-city study with strong PM associations in single-pollutant models also found associations with other pollutants (ozone and NO₂), though the NO₂ estimate was substantially reduced when modeled with PM_{2.5} (but not vice-versa). Other notable findings include a strong association between PM_{2.5} and diabetes mortality, as well as all-cause mortality in diabetics (Montreal) and an association of PM with air pollution modified by the socioeconomic characteristics of the population (Hamilton).

The NMMAPS in the US has provided a wealth of information on the acute health effects of exposure to air pollution. In the more recent literature, researchers have investigated additional details of this database. In two NMMAPS studies PM₁₀ was associated with increased cardiovascular/respiratory mortality, an effect that was greater than that for total mortality or other-cause mortality. This association generally occurred at lag 1 d and was stronger in the northeast and in California than in other areas of the country. When NMMAPS data were analyzed for potential biases associated with GAMs, it was concluded that there was little sensitivity to different data treatments (e.g. GAM vs. GLM). A series of studies were performed on this large database to assess a number of factors in the associations with PM: these indicated (among other things) that PM effects on mortality were significant all year round, that weather variables could not explain the observed associations with PM, and that results were robust when sampling frequency error (some cities in the analysis had only every-sixth-day PM readings) and potential exposure misclassification errors were addressed.

Even though the great majority of the reported studies have relied on ambient air monitors to reflect individuals' exposure to PM health effects, a few researchers have conducted analyses

using more precise exposure estimates. Such studies have examined within-city variation in exposure, monitor proximity, exposure distribution and source-influenced monitors to determine if a finer examination of the ambient monitoring produced differential results. In most cases these yielded increased risk estimates, usually with narrower confidence intervals.

The potential for mortality displacement (sometimes referred to as harvesting), though difficult to study, has been investigated by a few groups. Overall, there is little evidence of mortality displacement, which posits that PM is merely advancing the mortality of already-frail individuals by just a few days; instead indications are that the effect of PM extends for multi-day to month-plus periods and the cumulative risks are considerably greater than those for any single lag-day indicator.

A number of studies have examined whether there are population-level thresholds for the mortality associated with short-term exposure to PM. Approaches have included the fitting of alternative models to describe concentration–response relationships, or segregating high from low pollutant days to determine if risk estimates differ. Applying these methods to the results of a number of large US and European multi-city studies, including those reviewed in the US EPA 2004 AQCD and in this assessment (Section 14.5.1.2), revealed no evidence of a clear threshold for acute exposure PM-related mortality. Instead, in these studies total and cardiorespiratory mortality were observed to increase monotonically with increasing PM concentrations, even at relatively low PM levels. Though there are limitations in the ability of these methods to detect thresholds at very low concentrations (due to exposure misclassification, relative paucity of data and model specifications), and in some cases the studies had limited statistical power to distinguish between linear and non-linear representations of the data, the current evidence supports a linear relationship with mortality throughout the concentration range observed as the most appropriate fit for the relationship.

14.9.2.4.2 Hospital admissions

Similarly to acute mortality studies, most studies (>75%) that focused on acute exposure hospital admissions (Section 14.5.2) reported positive and significant associations with PM. The single-pollutant effect estimates from the multi-city studies with PM₁₀ ranged from 0.3% to 2.54% for various respiratory endpoints, and from -0.25% to 4.56% for cardiovascular hospitalizations, for a 10 µg/m³ increase. The corresponding values for PM_{2.5} ranged from 0.91% to 6.44% and from 1.28% to 9.75%, respectively. Associations between ambient PM and hospital admissions generally did not display marked seasonality. These associations were identified under various environmental conditions, using different data treatments (e.g. time-series vs. case-crossover) and PM metrics, although PM₁₀ and PM_{2.5} were the two dominant size fractions examined.

As was the case for mortality, a significant number of the newer studies examined more specific causes and categories of admission to hospital (sections 14.5.2.2 and 14.5.2.3). Acute exposure to PM was often more significantly associated with adverse outcomes in older adults (e.g. admissions for cardiovascular outcomes, stroke, CHF and MI). For respiratory conditions, susceptible populations included those with asthma (especially children) and/or COPD. Compared with previous assessments, newer studies tended to focus on more specific definitions of hospital admissions (e.g. ischemic stroke vs. hemorrhagic stroke; fatal and non-fatal MIs, CHF or IHD, with or without prior diagnoses) and indicated that these often yielded higher risk estimates, though this was not the case in all studies. There were some studies of more novel PM metrics (e.g. ultrafine mass, particle number count), though these provided equivocal results.

In the US NMMAPS study, some evidence of geographic heterogeneity (especially east–west) of overall effect was observed, with individual cardiac and respiratory outcomes themselves

exhibiting various degrees of geographic variability. However, formal statistical tests of heterogeneity in fact indicated little objective evidence of this, though it was acknowledged that the power to observe this phenomenon was limited. While the study indicated a significant association between PM and hospital admissions, the authors speculated that any differential relationships could have been the result of geographic variation in PM composition, overall pollution mix (and sources), and variance in socioeconomic factors.

The possible role of co-pollutants in PM-related associations with hospital admissions was examined in a minority of the reviewed studies. In most of these, the association with PM remained positive and statistically significant in multi-pollutant analyses with one or more of SO₂, NO₂, CO or O₃. There was some indication in these studies that PM-related effects are more robust in models with O₃ (with which PM is often not strongly correlated), and least robust in those with NO₂ (with which the correlation is often relatively strong).

Only a small number of recent Canadian studies were identified, most single-city. While these studies found associations with PM, they were often sensitive to the inclusion of co-pollutants. Positive and significant findings were observed when examining children and older adults and specifically with asthma- and COPD-related hospital admissions.

A limited number of recent studies have examined the shape of the exposure–response relationship between PM and cardiovascular hospital admissions. The results of these have indicated that the association is consistent with a linear or near-linear model, with no evidence of a threshold, thereby supporting the findings of earlier assessments.

14.9.2.4.3 Emergency room and other medical visits

Recent ERV data generally supported findings from respiratory hospitalization studies, as increases in ambient PM levels were associated with significantly increased visits to emergency rooms for respiratory causes as a group, or for individual causes (Section 14.5.3). Since ERVs for endpoints such as asthma attacks and respiratory illness are more frequent than hospitalizations, they usually generate larger databases. It is therefore easier to investigate specific diseases (e.g. asthma, COPD) rather than broad disease categories such as “respiratory diseases.” The new studies validate earlier research showing a strong relationship between PM and visits to the emergency room or to medical clinics due to specific respiratory health effects. The strongest PM-related associations were observed with asthma ERVs and to a lesser extent with COPD.

Studies of pollution-related health effects and primary care settings (see Section 14.5.3.4) suggest that measurement of access to the health care system outside of ERVs may provide additional and stronger evidence of these effects. In the limited number of these studies, PM was associated with respiratory endpoints diagnosed during doctors’ house calls, visits to family practitioners and in primary ambulatory care settings.

Physiologically, children may be more at risk from exposure to PM since their lungs are under development, their body’s immunological defences are not fully mature and they have more respiratory infections. Additionally, since they are generally outside for longer periods and are usually more active than adults, they may be more susceptible to the effects of ambient PM. In the small number of studies directly examining children, results indicated that while adults in the study were affected, children suffered greater impacts. In one study significant associations were reported for children’s respiratory visits in an ambulatory setting for several health conditions (asthma, URTI and LRTI) with various PM metrics (EC, OC, PM₁₀, PM_{10–2.5}, PM_{2.5}, UFPs), whereas for adults positive and significant results were only found for asthma visits in relation to UFPs.

Only one study published before 2002 investigated the relationship between PM and ERVs for cardiovascular outcomes. Since then, eight new studies have noted positive associations of PM, most often significant, with daily cardiovascular ERVs for all CVDs, ischaemic or hemorrhagic stroke, CHF, dysrhythmia and cerebrovascular diseases. Studies examining age-stratification of cardiovascular results yielded equivocal findings: given the age-stratification of CVD, one would expect to find greater impacts in older groups; however, this is not consistently evident in studies to date.

Because of the various PM metrics (PM_1 , $PM_{2.5}$, $PM_{10-2.5}$, PM_{10} , BS particles and TSP) used in the ERV and other medical studies it is not possible to draw specific particle-size-related conclusions, although these studies do consistently show an association between PM and acute respiratory diseases, especially asthma. Earlier work suggesting linkages between PM exposure and medication use has not been replicated by more recent studies.

14.9.2.4.4 Panel studies

As reviewed in Section 14.5.5.2, respiratory effects in asthmatics have been investigated in a number of panel studies, in which there were positive and often statistically significant associations between ambient concentrations of PM_{10} and/or $PM_{2.5}$ and decrements in PEF and/or FEV_1 , or increases in respiratory symptoms such as cough, phlegm, difficulty breathing, and bronchodilator use. These effects were most pronounced in asthmatic children, though adult asthmatics have been little studied. In several more recent studies, personal exposure of asthmatic children to $PM_{2.5}$ was associated with reduced lung function, sometimes more strongly than with the corresponding ambient concentrations. Three of four more recent studies provided some evidence for increased susceptibility to declines in lung function or increases in respiratory symptoms in asthmatic subjects taking maintenance medications compared with those not taking medication, perhaps because users are more likely to be subjects with more serious asthma. Associations between ambient PM_{10} and/or $PM_{2.5}$ and increased reliever asthma medication use were also reported, though not in all studies. Studies of non-asthmatics indicate that the effects on respiratory symptoms are similar to those in asthmatics, but lung function decrements are not observed as consistently. The results of several recent studies suggest that subjects with COPD may be at greater risk for PM-associated lung function decrements, but not for medication use or respiratory symptoms.

Cardiac arrhythmias and other disturbances in cardiac rhythm have been increasingly examined in more recent panel studies and are reviewed in Section 14.5.5.4. Although the variety of endpoints and populations studied makes it difficult to generalize, ambient $PM_{2.5}$ was related to ventricular and/or supraventricular arrhythmias/ecotopy, and ECG abnormalities (S-T segment depression, T-wave amplitude depressions) in several studies of subjects with or without cardiopulmonary conditions. Decreases in measures of HRV (a predictor of increased cardiovascular mortality and morbidity) have been associated with increases in ambient $PM_{2.5}$ or PM_{10} in most studies of elderly subjects with pre-existing cardiovascular conditions, and in a small number of studies with other categories of subjects (COPD patients, healthy young or elderly adults). Heart rate was also associated with ambient PM, most often positively, in panel studies of elderly subjects with or without heart disease. Vascular reactivity, an important indicator of vascular risk, has recently been examined in a few studies with results indicating a possibly potent effect of PM. While more work is needed, this effect appeared in Type II diabetics (but not Type I) and in others with a predisposition to cardiovascular effects. In contrast, there was no consistent association between ambient PM and blood pressure in a small number of panel studies of subjects with various cardiopulmonary conditions.

Evidence of PM-associated alterations in the levels of biomarkers (see Section 14.5.5.3), especially biomarkers of inflammation or blood coagulability, continues to emerge from panel

studies. The recent literature suggests a fairly consistent association between FeNO (a marker of airway inflammation) and exposure of asthmatic subjects to PM air pollution. PM-related increases in FeNO in asthmatic children, the most studied group, occurred earlier and were more pronounced than those observed in older adults, including subjects with COPD, asthma, or both conditions. The results of recent studies continued to indicate that significant increases in CRP (a marker of inflammation, tissue damage, and infections linked to increased risk of coronary events) were associated with PM (most often PM_{2.5}), in various groups of subjects, including in young healthy males, healthy older subjects, and older subjects with diabetes, obesity or hypertension. PM-related changes in several biomarkers associated with pathways leading to coronary events were observed in older subjects with CHD in a recent European study, including increases in CRP (inflammation), prothrombins (coagulation cascade), and vWF (platelet adhesion). These results extend earlier studies implicating ambient PM as likely contributing to increases in CRP, blood fibrinogen levels, and blood viscosity, and they provide some mechanistic support for the adverse cardiac effects associated with PM in the population-based epidemiological studies.

The possible role of co-pollutants was not investigated in the majority of panel studies. However, in the small number of studies in which this was examined, associations with lung function and with asthma symptoms remained after adjustment for other pollutants.

In a small number of panel studies, the ambient and non-ambient components of personal exposure to PM were estimated separately for each participant. Ambient PM was associated with health effects (on lung function, blood pressure, heart rate, SVE heartbeats and exhaled NO), whereas non-ambient and/or total PM were not associated with any health endpoints. These studies provide support for the use of ambient concentrations of PM as a surrogate for ambient exposure, demonstrate the usefulness of separating total personal exposures into their ambient and non-ambient components, and confirm that exposure to non-ambient PM will not confound the association between ambient PM and health effects.

14.9.2.4.5 Chronic exposure mortality

With few exceptions, the review of recent chronic mortality studies has revealed a consistent link between chronic exposure to various particulate pollutant metrics and total, cardiopulmonary and cardiovascular mortality, with indications of a significant relationship with lung cancer mortality. The new epidemiological literature significantly strengthens the existing evidence regarding the association between long-term exposure to PM and mortality. These results have come from reanalysis or extended analysis of existing cohorts, as well as from new datasets. The original results from the Harvard Six Cities and ACS cohorts have been reaffirmed in reanalysis, while providing a range of important new results as additional years of data and new approaches to analysis have been added. Reanalyses of these studies with additional models and methods indicate that the risk estimates for fine PM and for sulphate are similar to or higher than earlier reports. One of the most important results of these analyses is that mortality is predominantly related to the fine PM size fraction, with coarse PM and gaseous pollutants generally showing little effect. A specific analysis of the Los Angeles, CA, component of the ACS cohort using a more detailed analysis of ambient PM levels significantly increased the risk estimate, possibly due to better exposure classification of subjects. This study found a higher risk for IHD mortality than for total cardiopulmonary or all-cause mortality. In the original analyses of these two studies, results were suggestive of a link between exposure to PM metrics (PM_{2.5} and sulphate) and lung cancer mortality. Reanalysis of the datasets has confirmed this result and in addition, these results were robust to model specification and adjustment for a wide range of covariates (e.g. smoking, diet, occupation) that could confound such a relationship. Other lung cancer mortality studies are less consistent on this outcome, though also having somewhat lower statistical power to see such effects.

A California cancer prevention cohort was analyzed for relationships with air pollution. While there was evidence of a decline in risk in the later years of the study, the overall risk for PM was significant. Uncertainties with respect to the classification of exposure limit the interpretation of the study. A cohort of veterans was also analyzed for air pollution relationships, and while an overall and significant risk with PM metrics was found, a somewhat stronger relationship was imputed for exposure to roadway pollution.

Two small Canadian studies of chronic exposure mortality were conducted in Hamilton, ON. Though limited by the size of the study populations, these studies attempted to improve the exposure estimation and characterize the socioeconomic aspects of the risk. In both cases the risk estimates were positive and significant for PM and were larger than that found in other studies. Socioeconomic factors were an important modifier of the relationship in one of the studies, with those classified as being in the lower strata having significantly higher mortality risks. Other studies also provide some evidence of this, though the overall database is insufficient to draw firm conclusions in this regard.

A number of European cohorts have also been examined for associations between chronic PM exposure and premature mortality. These studies found associations with all-cause mortality, with the relationships being increased in size and robustness when focused on cardiopulmonary-related outcomes. Within this classification, IHD and CHD exhibited even higher risk associations.

Overall, a strong and coherent relationship has been established between indicators of chronic exposure to PM pollution and premature mortality. While most studies found this relationship with all-cause and cardiopulmonary causes of death, studies that examined more precise categorization of the mortalities found greater risks associated with specific cardiovascular outcomes such as IHD. Moreover, ambient concentrations of PM in the studies reporting significant associations were relevant to those in Canada. Respiratory mortality (not including lung cancer) was seldom examined as a specific outcome, and while there are occasional positive and significant results, overall there are insufficient results to draw conclusions with respect to this cause of death based on the literature reviewed in this assessment.

14.9.2.4.6 Chronic exposure morbidity

The review of recent studies of chronic morbidity associated with PM exposure provides evidence of an association between particulate air pollutants and cardiovascular and respiratory outcomes. With one exception, all studies performed in North America and Europe reported positive results for relationships between fine PM and both cardiovascular and respiratory adverse effects; as well, most results were statistically significant.

Studies that observed positive associations between PM exposure and chronic morbidity were performed using various methodological approaches, such as cross-sectional, prospective or retrospective cohort designs. Moreover, ambient concentrations of PM in the studies reporting significant associations were relevant to those in Canada.

Previous findings had supported a relationship between fine PM and chronic respiratory disease and lung function. Newer studies provide additional support for these, with significant insight into the relationship with children's respiratory health. Perhaps of most importance, findings from the California Children's Health Study add support to previous conclusions that chronic exposure to fine PM is associated with decreased lung function growth. While associated with multiple pollutants, including PM, there was evidence in this study that if exposures remained constant, this reduction was carried through into adulthood with resultant long-term consequences. However, evidence also indicated that for children moving from high pollution to low pollution areas before the end of adolescence, lung function growth could recover. Reductions in lung

function also appear to be related to long-term exposure to PM, although in the single recent study reporting such a relationship, several other pollutants also displayed similar relationships. In all studies of childhood bronchitis, a positive and significant relationship was found with PM. Where alternative pollutants and PM metrics were examined, PM remained a predictor of such effects, but measures of EC and traffic exposure provided as good or better predictors of increased risk. In the California Children's Health Study, there were clear indications of a synergistic effect of PM with endotoxins (as characterized by pet ownership) on the prevalence of bronchitis. Besides bronchitis, a number of studies examined the associations between chronic exposure to PM and a range of respiratory symptoms. General ear, nose and throat complaints exhibited a significant relationship with PM_{2.5}, and there was a specific relationship with otitis media, a common childhood illness. Prevalence of allergy and wheeze were also positively and significantly associated with exposure to PM, though in many cases the relationship was stronger for EC and measures of traffic exposure than for PM mass.

While adults have also been the subject of some investigation, the studies are much less common than for children. COPD patients appear to suffer from lung function deficits in relation to PM exposure, though there were few signs of respiratory symptom increase. For healthy adults, effects were more strongly associated with other pollutants or were absent.

Increasing attention is being paid to cardiovascular outcomes. Most notable among the new findings was a study in which CIMT, a recognized quantitative measure of atherosclerosis, was associated with fine PM. This result provides evidence of adverse effects of chronic exposure to fine PM on the cardiovascular system and a plausible subclinical link to the more serious cardiovascular morbidity and mortality that have been reported.

Finally, reproductive outcomes have gained increasing attention recently, with indications that air pollution is associated with fetal growth reduction, LBW, and in a few cases, infant mortality. While potentially very important, these results require additional investigation, as there are multi-pollutant associations, indications of a threshold, and a need to more fully investigate associated issues related to socioeconomic status.

14.9.3 Weight of Evidence for Various Categories of Effects

14.9.3.1 Introduction and Criteria for Causality

Air pollution epidemiology studies provide highly relevant evidence of the adverse health effects of PM, since they investigate responses in the general population (including susceptible subgroups) in "real world" settings. They also examine more serious health outcomes and/or very large numbers of people. Such studies have formed the basis for causal associations made in the past even though they are observational rather than experimental, and the information on both exposure and effects is generally only available for the population rather than individuals. However, exposure analysis has indicated that the daily average of personal PM among subjects is highly correlated with PM from ambient monitors—an important observation for population-based time-series studies in which population-average ambient concentration is related to the number of adverse events among the population.

Until relatively recently, toxicological and controlled human exposure studies were limited in their relevance for a variety of reasons. The use of artificial particles provided only limited insight as to the toxicity of real-world particles, the latter which have a highly heterogeneous nature, convoluted surface area, and active chemistry. Particle concentrators that are able to create laboratory atmospheres from outdoor air have become available and provide more relevant data from toxicological investigations with animals and human volunteers. Ethical and practical considerations continue, however, to limit the situations that can be investigated in experimental

settings. Panel studies, which involve the analysis of the response of small groups of individuals engaged in relatively normal activities, have provided a significant amount of evidence on the manner in which humans respond to exposure to ambient PM.

To evaluate the weight of evidence that the epidemiological associations between health outcomes and PM_{2.5} are causal, it is necessary to examine the various lines of evidence in combination and to assess the collective evidence using established criteria for causal determinations. In this section, the evidence for various categories of health outcomes is reiterated in an integrated fashion, by reporting the findings from the available epidemiological, controlled human exposure and animal toxicology studies together. This collective evidence is then evaluated for various categories of health outcomes in light of considerations that have traditionally been used to form judgments as to how likely it is that the observed associations are causal.

These considerations include

- the *strength of the associations*, including the magnitude and precision of the risk estimates and their statistical significance;
- the *robustness* of the associations to model specifications and adjustment for potential confounders such as weather, temporal trends, and co-occurring pollutants;
- the *consistency* of reported associations across studies and study designs conducted by different researchers in different locations and times;
- the *biological plausibility* of the associations in light of what is known regarding PM exposure and dosimetry and the types of effects observed and associated potential mechanisms of action; and
- the *coherence* of the relationship between exposure to PM and related endpoints within and across animal toxicology, controlled human exposure, and various types of epidemiological studies.

The above considerations are then used to conclude whether the association with a given health effect or related set of health effects is causal, likely to be causal, suggestive of a causal relationship, or inadequate to conclude that the relationship is causal.

The evidence that specific subgroups of the general population are more at risk to health effects, by virtue of increased exposure and/or susceptibility, is also considered in this subsection, and the shape of the concentration–response relationship between PM and health effects is addressed in subsection 14.9.4. These both have implications for the weight of evidence and the public health significance of the effects that are associated with PM.

14.9.3.2 Respiratory Morbidity and Mortality Associated with Acute Exposure

14.9.3.2.1 Lung function

The strongest evidence for the effects of PM on lung function comes from epidemiological studies that examine the relationship of pulmonary parameters to PM levels in panels of people engaged in normal activities. While such studies have been conducted for various groups, the primary focus has been on asthmatic children, with additional work on older adults with COPD. For asthmatic children, ambient PM measures (mostly PM₁₀ and PM_{2.5}) have demonstrated clear associations in most studies. Studies that use estimates of personal exposure instead of fixed site monitors reveal a consistently larger effect. As well, for those children classified as having more severe cases of asthma (usually based on medication use), greater effects are seen. There are also indications from a few studies that the presence of an upper respiratory infection confers even greater sensitivity to the effects of exposure to PM on pulmonary

function. In the limited number of multi-pollutant analyses, PM generally remained significantly associated with the effects on lung function, though in some cases the effects of the other pollutants (most notably ozone and NO₂) were somewhat greater. For older adults with COPD, there are also indications of adverse impacts on lung function measures, although the responses appear somewhat less than for asthmatic children. Non-asthmatic children and adults also show some lung function sensitivity in relation to PM exposure; however, the number of studies is small and the responses variable. Some support for these findings is found in studies of human volunteers' controlled exposure to CAPs, though the number of studies is limited, the exposure levels relatively high and the results variable. In studies with laboratory animals, there is evidence of PM-induced reductions in some pulmonary function measurements, impaired clearance mechanisms, and AHR.

14.9.3.2.2 Respiratory symptoms

As is the case for lung function, the primary evidence for an effect of PM on respiratory symptoms is provided by panel studies. Such studies have focused on children, especially those with asthma; as well, there has been some work with adult COPD sufferers and a limited number of studies of adults with other chronic diseases. Respiratory symptoms such as cough, chest tightness, rhinitis, shortness of breath and general asthma symptoms were positively and significantly associated with exposure to PM in asthmatic children. As was the case with lung function, measures of personal exposure usually provided evidence of greater effects than did exposure measures based on fixed ambient monitors. Similarly, children judged to have more severe cases of asthma appeared to be more sensitive to PM, although there was also an indication that regular medication usage could prevent or reduce the onset of symptoms. Healthy children, examined in a few studies, also exhibited similar respiratory symptoms in relation to PM exposure. Adults with COPD, while demonstrating reduced lung function parameters in response to PM exposure, did not suffer from greater rates of respiratory symptoms. In the few studies with healthy adults, respiratory symptoms were likewise not related to PM exposure. A small number of studies examined the respiratory effects of PM among adults with diagnosed cardiac conditions. In these, significant increases in respiratory symptoms (cough, shortness of breath) were observed in association with increasing PM exposure. Only a limited number of studies included multi-pollutant analyses, with results generally maintaining the relationship with PM, although the respiratory effects were sometimes equally or more strongly associated with other pollutants (CO, ozone)..

14.9.3.2.3 Lung injury and inflammation

A large and complex database has developed in relation to the impacts of PM on lung inflammation and injury. Regarding impacts on humans, the primary indications of effect are derived from panel studies, many of which are the same as those evaluating respiratory symptoms. The most consistent effects on inflammatory mechanisms are revealed by studies that examine FeNO measures, a sensitive marker of pulmonary inflammation. Overall, there is evidence that a number of different PM metrics, including PM_{2.5}, are associated in a dose-dependent manner with inflammation in the airways. These associations are found with personal, ambient and central site monitor measures of PM, and are also associated with other pollutant measures, especially some NO_x species. Such associations have been noted for asthmatic children and adults, with the effects appearing to manifest more quickly in children. Controlled human exposure studies also provide some evidence of effect, but are limited in number. In these cases, mild lung and nasal inflammation is elicited with CAPs, though results can be inconsistent. Some of this inconsistency may relate to the character of the particles used, since animal toxicology studies of inflammatory biomarkers appear to indicate that effects are more likely with complex combustion-related PM and/or particles with higher metallic content.

Toxicological work with animals and cell lines has blossomed in recent years and provides evidence to support a complex multi-pathway pulmonary response upon exposure to PM. Past studies indicated that PM elicited inflammatory responses as signalled by the influx of neutrophils to respiratory surfaces. Newer research confirms this and provides evidence that these responses occur in both healthy and diseased lungs. Additional results indicate that a variety of inflammatory pathways are invoked by PM and that a variety of PM constituents (e.g. metals, OC and EC, surface area indicators) are implicated in this. As well, there are indications that immunological defences are modified, with reduced ciliary clearance and greater resultant bacterial burden. Day-to-day, seasonal, and source-oriented variations are apparent, although all these may reflect variation in PM constituents. Tissue injury, as measured by fibrosis, epithelial dysfunction, protein infiltration and other measures, is also induced by many different PM types and constituents, both soluble and insoluble. Work with cell lines also provides evidence of situational variance in PM toxicity and inflammation. While much of this evidence provides indications of the toxicity of soluble fractions (such as surface-bound metals), there are also indications that the insoluble core can elicit a different set of reactions. Finally, the induction of oxidative stress has been demonstrated for a variety of PM types, with subsequent impacts on inflammation and cell damage. Pretreatment with antioxidants reduced or blocked such effects and provides an indication that oxidative stress could be an important underlying mechanism in these outcomes.

14.9.3.2.4 Emergency room and other medical visits

A greatly expanded database of studies investigating emergency room and other medical visits in relation to PM exposure has accrued since the time of the last Canadian PM assessment. Newer studies have built on the earlier indications of PM effects on ERVs and added some data on doctors' visits and other types of medical visits. For general respiratory classifications, results indicated increased ERVs in relation to ambient PM levels, with almost all studies reporting positive relationships that were often statistically significant. Regarding asthma-related visits specifically, all studies reported positive and significant associations, for both children and adults. For children, especially those under the age of five, additional associations were in evidence for respiratory infections (upper and lower) and for pneumonia. For older adults, COPD-related visits were sometimes associated with PM levels, although the relationship was not consistent. Few studies examined multi-pollutant issues, with the limited results providing variable impacts. The small number of studies examining seasonality of effects provided evidence of year-round effects, with some instances of enhanced effects during cooler periods. There were also some indications that biomass burning in cities and forest fires exhibited particular linkages with medical visits, though the number of studies was limited. Longer lag periods appeared to be associated with significantly larger risks, though again the number of studies was small. There were few new Canadian studies; however, most of the newer studies were conducted in areas with ambient concentrations relevant to Canada.

14.9.3.2.5 Hospital admissions

As with ERVs, there is a much expanded database of studies of hospital admissions in relation to PM levels, with many of these being conducted in Canada. Earlier studies had indicated that general increases in respiratory hospital admissions were associated with ambient PM levels, with evidence that risks were greater for specific diagnoses such as asthma and COPD. These results have been affirmed in newer studies, with general respiratory admissions exhibiting positive and significant associations with ambient PM levels, and greater risks for specific outcomes. COPD was the most studied outcome examined, but similarly significant relationships were exhibited for pneumonia, upper and lower respiratory infections, and bronchitis. While there was evidence of some likelihood of effect of PM in all age groups, including children, those over 65 demonstrated greater sensitivity for most outcomes. As for

ERVs, there was evidence of co-pollutants attenuating the effects of PM, although in most cases, PM relationships remained significant. The coarse fraction of PM₁₀ can sometimes elicit effects of a similar magnitude to PM_{2.5}. However, in studies where the two fractions could be directly compared, the fine fraction appeared to be more potent. Effects were largely shown to be year-round, with indications of some elevation in the summer that could be attenuated by assessing indicators of air conditioning usage.

14.9.3.2.6 Premature mortality

Mortality associations with PM have been examined over many years, with recent additions to the literature focusing on multi-city studies (which have advantages over single-city studies) and increasingly on groups of outcomes (respiratory and cardiovascular vs. all-cause) and specific outcomes (e.g. pneumonia). These studies revealed a consistent set of significant associations between mortality outcomes and acute exposure metrics for PM. Studies of combined cardiorespiratory mortalities indicated elevated relative risk due to PM exposure vs. those considering all-cause mortality. The risk of respiratory mortality is elevated over total cardiorespiratory risk, with limited evidence that specific outcomes such as pneumonia are of greater importance. Additional evidence indicates that individuals with COPD may be at greater risk for cardiovascular-related premature mortality. While there is some indication that the elderly are somewhat more sensitive, risks also appeared in younger age groups. In many studies, inclusion of co-pollutants (especially NO₂) attenuated the relationships, though in most cases these remained significant. Most studies used ambient measures of PM₁₀; however, other metrics appeared equally associated with the outcomes. Mortality associations with PM levels showed little seasonality, being similar in all-year analyses and in the small number of seasonally restricted analyses. Although recent studies also provided some evidence of an influence of socioeconomic factors, these were insufficient to draw conclusions at this time.

14.9.3.2.7 Conclusions for acute exposure respiratory effects

Panel studies of individuals engaged in normal activity in ambient settings demonstrate that current levels of PM_{2.5} (and other PM metrics) are associated with a variety of effects, including reduced lung function, increased respiratory symptoms and pulmonary inflammation. Asthmatic children and adults with COPD appear to be most susceptible to these effects, though there is limited evidence that healthy children and adults may be at some level of increased risk. For asthmatic children, indications of the character of the underlying condition appear to be related to the effects, with more severe asthma conditions imparting greater sensitivity to the PM impacts, though there are some complex interactions apparent when medication use by asthmatics is examined. Existing respiratory infections as well as pneumonia also appear to impart greater susceptibility to the effects of PM exposure. These relationships show some sensitivity to the inclusion of co-pollutants in the analysis, with effects for PM being often reduced, though not removed. Studies with human volunteers in controlled exposure settings provide some limited support for the identification of asthmatics as a sensitive group, though results from this area of research are currently limited. Animal toxicology provides support for the lung function effects seen in panel studies; however, the main contribution from this line of research is in its observations related to lung inflammation and injury. Such research indicates that a multitude of biochemical pathways are invoked upon exposure to PM, leading to pulmonary inflammation, tissue damage, and immunomodulation. There are also indications in this work of significant variability in response from particles collected at different times and locations, with implications for the heterogeneity of results seen in some human studies. Oxidative stress from such particles appears to be an important mechanism that potentially underlies many of the effects observed.

Overall, PM is implicated in a variety of human respiratory effects, with mechanistic explanations for such effects being provided by toxicology studies. The observation of increased medical interventions, including doctor's visits, ERVs and hospital admissions, is consistent with these effects, especially considering the convergence of the evidence of effects among asthmatic children and persons with COPD, and the appearance of existing respiratory infection as an aggravating factor. Thus, based on evidence from several lines of enquiry exhibiting strength of association, robustness, consistency, biological plausibility and coherence, there is a basis for concluding that there is **a causal relationship** between respiratory morbidity and acute exposures to PM_{2.5} that results in increased respiratory ERVs and hospital admissions.

The mechanisms that appear to underlie acute PM morbidity are also applicable to acute exposure mortality. While PM appears to increase all-cause and cardiorespiratory mortality, the identification of those with respiratory infection as being particularly vulnerable in mortality studies is consistent with a progression of the inflammatory, cell damage and biochemical mechanisms observed upon acute PM exposure, and the morbidity outcomes described above. Thus, based on strength of association, robustness, consistency, biological plausibility and coherence, the overall evidence indicates that there is **a causal relationship** between acute exposure to PM_{2.5} and respiratory mortality.

14.9.3.3 Respiratory Morbidity and Mortality Associated with Chronic Exposure

Past research provided evidence that chronic exposure to fine PM exhibited some significant associations with adverse respiratory effects, especially for children. These effects included increased prevalence of chronic bronchitis, reduced lung function growth and reduced lung function measures. More recent work provided support for these findings, with indications that bronchitis symptoms for asthmatics were more prevalent with increased levels of PM_{2.5}, but occurred with increased levels of NO₂ and ozone as well. While some of the relationships remained positive and significant in multi-pollutant models, others were reduced. Pulmonary function measures were also reduced with chronic PM exposure, but as for the above symptoms, similar relationships were also evident for other pollutants, such as NO₂ and acid aerosols. Other respiratory issues (e.g. otitis media, ear/nose/throat complaints, wheeze) have been associated with long-term exposure to PM, although the database for specific outcomes is relatively small. In many of these cases, the effect of fine PM was not sensitive to inclusion of gaseous co-pollutants, but risks were sometimes greater with markers of traffic exposure. In laboratory animals, some evidence is available for effects of chronic exposure, including indications of hyperplasia and fibrosis, although these were elicited at high concentrations. Thus, while the available evidence demonstrates aspects of biological plausibility and coherence, the possible role of other pollutants and the relatively small number of studies indicates that the overall database is **suggestive of a causal relationship** between chronic PM exposure and respiratory morbidity.

A variety of studies, including many of high quality, have examined premature mortality and chronic exposure to PM. While many of these present evidence of significant associations for cardiopulmonary mortality, relatively few have examined respiratory mortality in isolation. Of those that have, there are sometimes findings of associations; however, these associations are not consistent and have not generally been subject to detailed analysis. Thus, current evidence is **inadequate** to draw any conclusions with regard to the causal linkages between chronic exposure to PM and respiratory mortality.

14.9.3.4 Cardiovascular Morbidity and Mortality Associated with Acute Exposure

14.9.3.4.1 Vascular function

Earlier animal and human toxicological studies on vascular function provided some evidence of increases in circulating inflammatory markers, increased potential for coagulation (and attendant thrombosis) and vasoconstrictor mediators. Newer toxicological and epidemiological investigations have provided substantially more information in this area. Work with panels of people engaged in regular or normal activities has become relatively extensive, and has examined individual and group response in a variety of biomarkers of vascular function in relation to ambient and personal PM (and other pollutant) measures. Healthy individuals appeared to show little response, while those with some form of pre-existing disease (e.g. diabetes, hypertension) demonstrated more consistent (though still variable) effects for inflammatory and vasoconstrictor indicators. A more comprehensive set of results provided indications that various PM metrics (including PM_{2.5}, BC, PN) appeared to increase vascular inflammation, vascular reactivity and blood coagulation potential (increased cellular adhesion). As for other markers of these effects, there was significant variability between studies (at least partly a result of variability between study conditions) though again, those with pre-existing disease (notably diabetics) had greater sensitivity to exposure. Various other factors, such as age, genotype, medication usage and BMI, also modified the response to PM. Studies in experiments with human volunteers, while not as numerous, provided supporting evidence for the effects seen in panel studies. Such studies used both laboratory-generated UFPs and CAPs, and indicated vascular inflammation and increased coagulation potential (increased cellular adhesion). Animal studies are also indicative of similar vascular effects, with consistent signs of increased inflammation, thrombosis, increased and impaired vasoreactivity, and up-regulation of the genes involved in these processes. Overall, the database provides evidence of a number of markers of effect that can initiate adverse cardiac processes.

14.9.3.4.2 Cardiac function

Limited previous research had indicated that PM could affect some measures of cardiac function, including heart rate, HRV and ECG parameters. While variable, such findings were hypothesized to be indicative of possible steps in a chain of events leading from PM exposure to adverse cardiac outcomes. More recent work has been extensive, and while providing support for these previous findings, it has also provided a more complex picture of events related to PM exposure. Evaluation of the response of implanted cardiac defibrillators with increasing PM levels in the US northeast indicated a significant relationship between ambient PM and the frequency with which these devices were activated in response to arrhythmias. Additional research in other geographic areas has not produced similar results. Many new studies have evaluated a range of specific cardiac function parameters, including cardiac rhythm, the frequency of arrhythmias, the presence of ectopic heart beats, heart rate and HRV. Significant alteration of cardiac rhythm was a consistent feature of these studies, with depression in several of the metrics that characterize this in association with increasing PM levels. The presence of a previous cardiovascular event or cardiovascular disease appeared to impart vulnerability to this group of outcomes, though relatively healthy subjects also showed effects. Higher frequency of arrhythmias was also associated with PM exposure, though in some cases the increases were confined to the higher quartiles of PM exposure. Ectopy (extra heart beats) was evaluated in a number of studies, and was increased significantly in association with PM concentration in virtually all cases. Groups of both healthy individuals and those with pre-existing disease were affected, though those with hypertension appeared to be significantly more vulnerable. While ectopy itself is not generally regarded as adverse, it is an indicator of a cardiac effect and is associated with increased arrhythmia, and the impact of ectopy on those with pre-existing disease is not clear. Heart rate has also been evaluated in relation to PM levels in a number of

studies, and both increases and decreases were shown in various settings with both healthy and compromised individuals. Hypertension appeared to impart greater sensitivity to increased heart rate. Reduction in HRV (a predictor of increased cardiovascular mortality and morbidity) was seen in the majority of studies, especially in those with pre-existing disease. Particularly sensitive groups included those with hypertension, ischemic conditions and COPD. Medication use could modify HRV reactions, as could the status of the GSTM1 gene. For most of the attributes evaluated here, many different PM metrics (PM_{2.5}, PM₁₀, PM₁, EC, OC) appeared to be related to outcomes. For heart rate and HRV, the complex interactions between the different PM metrics and various aspects of the heart rate parameters suggested multiple independent pathways by which PM could exert effects. When evaluated, some gases (NO₂ and CO but not ozone) were also associated with outcomes, although in general they did not appear to reduce the association with PM in the limited number of multi-pollutant models run.

14.9.3.4.3 Emergency room visits

Evaluation of cardiovascular outcomes in earlier ERV work related to PM was relatively rare. Though still constituting a small database, newer studies have provided indications of PM-related cardiac conditions requiring medical treatment. Stroke was evaluated in a number of studies and demonstrated a significant relation with PM levels, especially for ischemic stroke. However, this type of stroke was also associated with markers of traffic pollution (NO₂ and CO), and in multi-pollutant models with these, the PM effect was somewhat attenuated. ERVs for general CVD, IHD and CHF were also associated with PM levels in ERV studies, with some indications that the associations were as good or better with particulate OC and EC constituents. NO₂ and CO in multi-pollutant models were also associated with ERVs, with the PM mass effect somewhat reduced. These overall results were found for adults as a group, with no consistent indication that elderly age groups were at greater risk.

14.9.3.4.4 Hospital admissions

Earlier studies had provided indications that PM₁₀ and PM_{2.5} were associated with hospital admissions, with some evidence of greater risks for certain types of cardiac disease. These associations were often independent of co-occurring pollutants such as NO₂ and CO, but there was also evidence that in multi-pollutant models, gaseous pollutants could reduce the PM effect or were indicative of additional effects. The database on cardiovascular endpoints has grown substantially, with investigation of specific cardiac outcomes in many studies. With few exceptions, these newer studies found significant associations of PM with cardiovascular hospital admissions. In turn, several specific categories of cardiovascular admissions had greater PM-related risk estimates, with ischaemic outcomes (both heart and stroke), MIs and CHF seemingly enhanced in relation to CVD hospitalizations as a whole. Additional evidence points to those with previous cardiac complications (such as previous MI) as being at even greater risk. While most of these studies examined PM₁₀, those that evaluated smaller particles appeared to show greater risk. From an age perspective, most studies were confined to the population over 64 years old, though evaluation of all ages combined also demonstrated similar elevated risks for CVD admissions. Many studies examined multi-pollutant relationships, and while often reduced, the risks associated with PM remained significant. The gaseous pollutants NO₂ and CO were the primary factor in this, while evaluations with ozone indicated independent effects. Of note in these studies, multi-city analyses uniformly demonstrated significant associations between PM and hospital admissions, while single-city studies showed somewhat less reliable (though always positive) results indicative of the greater statistical power of multi-city studies. While the risks of both cardiovascular and respiratory admissions with increasing PM levels were elevated over more general categorizations, the former appeared somewhat stronger when comparisons were available, although pre-existing respiratory conditions seemed

to raise cardiovascular risk. Associations were generally not sensitive to seasonal analysis (i.e. the effect was consistent year-round).

14.9.3.4.5 Premature mortality

A considerable body of literature linking short-term exposure to PM and premature mortality from total, cardiopulmonary and cardiovascular causes has existed for some time. This evidence had demonstrated significant associations, although there were indications of effects from some gaseous pollutants (most notably NO₂, with the PM effect often attenuated (but not eliminated) in multi-pollutant models). Multi-city studies provided some indication of heterogeneity across regions, evidence of a greater effect on cardiovascular mortality, and increased risk when multi-day exposures were considered. A significant increase in supportive toxicological research on mechanism of action has also evolved. The more recent epidemiological work provides very similar evidence, with some refinements on critical exposure windows and specific cardiac outcomes. As was seen with hospital admissions data, conditions related to IHD, CHF and MIs were more likely to lead to premature mortality associated with PM, and those with pre-existing respiratory conditions (especially pneumonia and COPD) were also at increased risk. Diabetics also exhibit markedly increased risk factors, consistent with both the underlying condition as well as the prevalence of cardiovascular complications with this disease. While single-day lags (0 or 1) provided the largest risk estimates, analysis of multi-day lags provided evidence of extended risk windows, with single-day lags underestimating the total PM impact. Multi-pollutant analyses (especially in relation to NO₂) continued to exhibit some attenuation of the PM effect, though positive and significant PM effects were usually maintained. While the elderly were the most studied age group, increased risk was apparent in more general age categorizations. Analyses using PM_{2.5} generally yielded greater risk estimates than those with PM₁₀, although the majority of studies were conducted using measures of PM₁₀.

14.9.3.4.6 Conclusions for acute exposure cardiovascular effects of PM

Epidemiological studies evaluating the relationship between ambient PM levels and hospital visits (both ERVs and admissions) and premature mortality find consistently significant associations, for both all-cause and cardiovascular outcomes. As might be expected, evaluation of cardiovascular outcomes provides evidence of greater risk than for all-cause in a range of study types. Specific diagnoses involving ischemic disease (both stroke and cardiac), CHF, and MI are of particular note within the category. The existence of previous cardiorespiratory conditions, especially hypertension, MIs, pneumonia and COPD appear to confer an extra level of sensitivity for both hospital admissions and premature mortality. Significant support for this is provided by panel studies in which PM has been noted to increase biomarkers of vascular coagulation and inflammation, as well as cardiac function. Animal toxicological experiments provide additional support, with clear indications of PM-instigated vascular inflammation, thrombosis and vasoreactivity and effects on cardiac function. Panel studies also identify those with hypertension, diabetes and ischemic conditions as being more reactive to the effects of PM exposure, especially but not exclusively in relation to cardiac function measurements. Heterogeneity of risk within multi-city studies has been noted, and it has been attributed to several factors, including variability in PM components and socioeconomic factors among other issues. Some support for this is found in panel and toxicological studies wherein different components or size fractions of PM impart different effects and invoke different biochemically relevant cardiac pathways. Other pollutants, especially NO₂ but also CO, have been noted to exhibit significant associations with these outcomes as well, and in some cases have attenuated the PM risk estimates. These co-pollutant associations have been hypothesized to represent particular sources, such as combustion or traffic, though they cannot be ruled out as independent effects. Cardiac function has been shown to be sensitive to other pollutants,

especially NO₂. While most studies have only evaluated the impacts on older adults, risks appear elevated in broader age categories, though higher in those over 65 years of age.

Overall, the consistent finding of elevated risk for hospital visits and premature mortality in relation to PM exposure, along with the supporting work from panel and toxicological studies, exhibits strength of association, robustness, consistency, biological plausibility and coherence for altered and impaired cardiovascular function and is indicative of **a causal relationship** between acute exposure to ambient PM_{2.5} and cardiovascular morbidity and mortality..

14.9.3.5 Cardiovascular Morbidity and Mortality Associated with Chronic Exposure

Disease resulting from chronic air pollution exposure is inherently more difficult to study than acute disease, and as such there are far fewer studies for both chronic cardiovascular morbidity and mortality outcomes. The primary evidence of effect comes from a series of studies that examined premature mortality in relation to long-term PM exposure, primarily in American settings. In all studies, measures of cardiovascular-related mortality risk with PM were greater than those for both all-cause mortality and respiratory mortality. Elevated mortality risks with PM exposure were noted for IHD, CHF, cardiac arrest and in some cases, for diabetics. Though the database is relatively small, the evidence indicates that PM_{2.5} is more strongly associated with these outcomes than PM₁₀ and that co-pollutants such as NO₂ and CO may slightly attenuate PM effects but do not reduce the statistical significance of the PM effect. SO₂ (or sulphate in some studies) is also associated with premature mortality. While studies of morbidity outcomes with chronic exposure are rare, a recent analysis provided evidence that long-term exposure to PM was significantly associated with a measure (CIMT) associated with atherosclerosis and increased cardiovascular risk. The panel and animal study findings of various cardiovascular perturbations provide mechanistic support for these findings, although they were largely collected in acute exposure scenarios. Chronic exposure work with compromised laboratory animals and CAPs provides clearer examples of mechanisms such as atherosclerosis progression, plaque inflammation and instability, as well as compromised cardiac and vascular status. These provide a basis for the biological plausibility of the effects seen in both the limited morbidity database and the more extensive chronic exposure mortality database. As such the evidence linking chronic exposure to CV mortality exhibits sufficient consistency, robustness, coherence and strength of association to be classified as **a causal relationship**, while the evidence for cardiovascular morbidity lacks some elements of coherence and strength of association but is **suggestive of a causal relationship**., .

14.9.3.6 Total Mortality

While this risk characterization has focused on specific respiratory and cardiovascular outcomes, all-cause mortality has been assessed in most studies, and until relatively recently was the primary outcome evaluated. Given the importance of cardiovascular mortality in overall non-accidental mortality, it is not surprising that acute and chronic exposure to PM is consistently associated with all-cause mortality, meets the criteria for causality and constitutes **a causal relationship** for this outcome.

The evidence presented here also leads to the conclusion that there is mortality associated with acute exposures to temporarily elevated levels, as well as to chronic exposure to PM. These mortalities appear to be rooted in different, but related, processes and are concluded to be separate outcomes. Analysis of studies such as the ACS and Harvard Six Cities cohorts indicates that chronic mortality substantially advances the date of death for populations. Acute exposure studies are not as amenable to such analysis; however, examination of the form of the relationship does not indicate that these mortalities are displaced by only a few days (the so-

called “harvesting hypothesis”), with longer multi-day to month-plus lags indicating increased impacts versus single-day maximum risk estimates.

Both acute and chronic exposure mortality studies have been conducted in Canada or at levels that are consistent with air quality conditions in parts of Canada. As such, it is concluded that premature mortalities, both acute and chronic in nature, are currently occurring in Canada.

14.9.3.7 Other Effects

A variety of other effects have been noted in a small but growing number of studies. While ostensibly a respiratory effect, mortality from lung (and other) cancer(s) is treated separately here. While only a few epidemiological studies have had the data or power to examine these outcomes, there are important indications that lung cancer mortality is associated with long-term exposure to PM. Animal studies done at high exposures provide some mechanistic plausibility for the ability of PM to instigate lung cancer, and the epidemiological findings are indicative of an effect on lung cancer mortality. Though this database is limited, the findings in the strongest studies to date are biologically plausible, show some strength of association and are relatively robust. Thus the available evidence for chronic exposure to PM indicates that there is **likely a causal relationship** with lung cancer mortality.

Several reproductive and development endpoints have been evaluated in relation to exposure to PM and other pollutants. These endpoints include postnatal mortality, preterm birth, IUGR, and LBW. While some associations with various metrics are noted, associations are often stronger with other pollutants such as CO and NO₂ as well as with roadway exposure metrics. Overall, the evidence to date on these outcomes is **suggestive of a causal relationship**. However, additional understanding of the multi-pollutant issues is necessary in order to better grasp the implications associated with these outcomes.

14.9.3.8 Subgroups with Increased Sensitivity or Exposure

Available evidence indicates that a variety of factors can affect individuals' responses to ambient PM. Some of these are innate factors that can affect the sensitivity of individuals to exposure to PM, such as certain pre-existing diseases. Other factors may render individuals more vulnerable to PM by increasing their exposure, for example time-activity patterns.

Individuals with pre-existing respiratory disease may be sensitive to the additional oxidative and inflammatory burden resulting from exposure to ambient PM. A number of lines of evidence indicate that asthmatics are a susceptible subgroup. In epidemiology studies, acute increases in ambient PM levels were consistently associated with asthma ERVs and with respiratory hospitalizations (including admissions for asthma in some studies that investigated respiratory subcategories). In panel studies of asthmatics, acute PM exposure was associated with decreased lung function and increases in asthma symptoms and medication use; in non-asthmatics there were effects on respiratory symptoms but lung function decrements were less consistent. In epidemiology studies of long-term exposure, ambient PM was associated with increases in the prevalence of some asthma-related symptoms (e.g. wheeze). Exposure to PM has induced AHR (the hallmark of asthma) in laboratory animals, and recent data from experimental allergy models have supported the concept that exposure to ambient PM may exacerbate allergic asthma.

There is also some evidence (albeit more limited than for asthma) that people with COPD represent a susceptible subgroup. In a number of population-based epidemiology studies, increases in ERVs, hospitalizations and mortality in patients with COPD were associated with short-term PM concentrations. The results from some panel studies indicated that subjects with COPD may be at greater risk for PM-related lung function decrements and effects on cardiac

endpoints. Though there are no specific COPD disease models in animals, chronic bronchitis in rodents was shown to enhance the inflammation and oxidative stress caused by PM inhalation.

A large body of evidence indicates that people with cardiovascular diseases are more susceptible to the health effects from ambient PM. Short-term exposure to PM was consistently and robustly associated with greater risks for cardiovascular mortality than those for all-cause mortality. PM-related increases in cardiovascular hospitalizations and ERVs have been reported in a large number of studies; moreover, risk estimates for specific cardiovascular causes (e.g. MI, CHF, IHD) were often considerably greater than those for cardiovascular causes as a whole. Similarly, in US and European epidemiology studies of long-term exposure to PM, increased risks were found for IHD and CHD compared with those for cardiopulmonary mortality, which were in turn greater than the risks for all-cause mortality. In panel studies ambient exposure to PM was associated with decreased HRV (a predictor of cardiovascular mortality and morbidity) in most studies of subjects with pre-existing cardiovascular conditions, and less consistently in studies of other subjects. PM-related changes in circulating levels of biomarkers associated with pathways leading to coronary events, including CRP, prothrombins, vWF, fibrinogen and blood viscosity, were also reported in panel studies. Finally, in studies of animal models of human disease, research with SH rats indicated that hypertension increased the susceptibility to the inflammatory and cardiovascular effects of PM, and work with ApoE^{-/-} mice indicated that their hypercholesterolemia and predisposition towards atherosclerosis increased their susceptibility to the cardiovascular toxicity of PM.

The results of several epidemiological studies have indicated that people with diabetes are also susceptible to the effects of PM, including mortality, possible due to cardiovascular complications associated with diabetes.

Age is also a determinant of susceptibility. Physiologically, children may be more at risk from ambient PM because their lung and immune systems are still maturing, and they generally are more exposed because they spend more time outdoors and are more active than other age groups. Consistent with this, a number of lines of evidence indicate that children are indeed more affected by exposure to ambient PM. In the small number of ERV/medical visit studies that directly examined children, children were at greater risk of asthma attacks and respiratory infections than were adults. Similarly, in panel studies, PM-related effects including increased FeNO were more pronounced in asthmatic children than in older adults with asthma or other respiratory diseases. In other panel studies, of healthy subjects, significant findings were generally limited to studies in children rather than adults. Chronic exposure to PM was also linked to chronic respiratory disease, respiratory symptoms, and decreased lung function in children, though adults have not been much studied.

The elderly are also susceptible to a number of the effects from exposure to PM, at least in part because this is the age group where the majority of the diseases that predispose to PM-related effects are most common. Epidemiology studies of short-term PM-related mortality have consistently revealed that risks for all-cause, cardiovascular or respiratory mortality were greater in older adults. In a number of studies of hospital admissions, acute exposure to PM was again more significantly associated with adverse outcomes (e.g. hospitalizations for cardiovascular outcomes, stroke, CHF, MI) in older adults than in younger adults. In panel studies, decreased HRV was reported in most studies of elderly subjects with pre-existing cardiovascular conditions, and less often in studies of other subjects. Similarly, decreased HRV was reported in controlled studies of elderly subjects exposed to CAPs, but not in a study in younger subjects. Research with animal models of hypertension and atherosclerosis also provides support for the elderly as a population that is susceptible to the effects of PM, given the high prevalence of these conditions in older age groups.

There is emerging evidence that genetics play a role in interindividual differences in susceptibility to PM exposure. Toxicological research in inbred mice has revealed that there are strain-specific differences in AHR, inflammation, AM phagocytosis and mortality from exposure to PM, indicating that some genotypes are more sensitive to the effects of particulate air pollution. A limited number of studies also provided evidence that certain genotypes (specifically with the GSTM gene group that is involved in detoxification) confer greater sensitivity to several adverse effects. This provides a plausible explanation for at least part of the range of responses seen in experimental studies in animals and humans.

Populations can also be more vulnerable to the effects associated with ambient PM if they receive greater exposures to the pollutant than the population at large. In earlier reports of the California CHS, risk estimates for respiratory effects related to long-term PM exposure were increased for the subset of children spending more time outdoors. In addition, acute PM-related effects on mortality or hospitalizations were increased in populations with less residential air conditioning use (and hence greater infiltration of ambient PM) in a number of studies. Numerous epidemiology studies have reported that adverse health effects are increased in relation to traffic pollution or proximity to major roadways, which are important sources of ambient PM exposure. Exercise can also increase deposition of PM in the respiratory tract through the higher breathing rate, larger tidal volume, and switch from nose breathing to mouth breathing with more intense activity, and the more rapid breathing of children also leads to greater deposition. In some studies, effect estimates for PM-related mortality and hospitalizations were increased in populations with lower measures of SES, though this effect modification was not consistently observed, and it is not clear whether it was the result of increased exposure or some other factor.

14.9.4 Shape of the Concentration–Response Curve

The shape of the concentration–response relationship between ambient PM and various health outcomes has implications for estimating health impacts from exposure to particulate air pollution and for risk management to address these impacts. This aspect of the association between PM and health effects, including the potential for the existence of threshold levels below which health effects are not observed, has been investigated in a number of studies.

Some studies have examined whether there are population-level thresholds for the mortality associated with short-term ambient PM using various approaches, including the fitting of alternative models of concentration–response relationships or the segregation of high from low pollutant days to determine whether risk estimates differ. Analyses of a number of large US and European multi-city studies reviewed in this and earlier assessments has revealed no evidence of a clear threshold for acute PM-related mortality. Instead, in most studies total and cardiovascular mortality increased monotonically in a quasi-linear manner with increasing PM concentrations, even at relatively low ambient PM levels. Statistical tests comparing linear and various non-linear and threshold models have not shown significant differences between them in goodness of fit to the data. An earlier analysis of mortality in relation to long-term PM exposure also revealed a quasi-linear association.

Similarly, a limited number of recent studies have investigated the shape of the concentration–response relationship between PM and cardiovascular hospital admissions. The results of these have also indicated that the association is consistent with a linear or near-linear model down to very low concentrations, thereby supporting the findings of earlier assessments.

The general lack of a clearly identifiable threshold at a population level based on the epidemiology studies is consistent with the range of susceptibility to the effects of PM among

individuals and between susceptible groups. Although individual thresholds may exist, they are likely to differ widely, particularly considering that the population-based epidemiology studies include subjects who have the most severe pre-existing disease and are therefore most likely to be affected by air pollutants at low concentrations. Due to large differences in sensitivity that are the result of this heterogeneity within the general population, a common threshold may well not be observable at a population level in epidemiology studies. In addition, a number of the disease conditions that are affected by ambient PM (e.g. asthma, hypertension, atherosclerosis) are common in the general population and are the combined result of multiple risk factors, including air pollution. The contribution of air pollution to these diseases would be expected to be additive to the existing burden they present in the general population, which affects a substantial proportion of the population (e.g. atherosclerosis begins in youth, increases progressively and is pervasive in adult populations; hypertension affects more than 30% of the population to some degree), without exhibiting any evidence of a population threshold. However, it is recognized that other factors may also make it difficult to identify a threshold at a population level, including low data density in the lower concentration range of ambient PM, measurement error resulting from differences between individuals in the relationship between personal exposure to PM and its ambient concentration, or model specifications.

14.9.5 Uncertainties in Assessment of Health Effects of PM

Despite the general coherence of the database concerning PM health effects, especially with the emergence of a considerable body of toxicological evidence in recent years, there remain important uncertainties in the understanding of the exposure and health effects of PM. PM itself is a complex mixture of substances and exists in the atmosphere as part of a complex mixture of pollutants, complicating the understanding of health effects. This section discusses the more important uncertainties in the database that has been used to characterize the risks associated with ambient PM in this review and that would be expected to contribute to risk management of PM. For each issue discussed, the uncertainties and their implications are briefly summarized.

- *Toxicity of PM as a function of composition, size, and sources*—Arguably, chief among these uncertainties is the influence of the exact chemical and physical nature of PM on adverse effects, and the degree to which different sources influence toxicity and health impact. Though the evidence is far from complete, emerging evidence appears to indicate that some constituents of PM (e.g. metals, EC and OC) elicit more toxicity than others or instigate particular adverse metabolic pathways. Better understanding of this issue could resolve some basic toxicological uncertainties, but more importantly could point to more cost-effective regulatory and exposure-reduction measures, or equally could indicate that broad-based actions remain the best approach to risk reduction.

—Related but somewhat separate, it is thought that PM from different sources also differs with respect to its toxicity, although to date no PM source has been demonstrated to be non-toxic. Combined with an improved understanding of component toxicity, information in this area could greatly inform a variety of risk management strategies and point to more cost-effective strategies for control. Such information might also resolve some of the apparent geographical heterogeneity evident in some epidemiological studies.

—A related uncertainty is that of particle size and physical characteristic. While health effects have been associated with both fine and ultrafine (and coarse) particles, the degree to which these are independent is unclear. Some basic parameters of UFPs (e.g. much greater surface area and active chemistry) would indicate that on some fundamental aspects, one would expect this size fraction to exhibit greater toxicity. Conversely, exposure studies of PM penetration indoors (where Canadians spend most of their time) indicate that PM above the

UFP range penetrates the building envelope more readily and should therefore potentially be more problematic. Toxicological evidence is equivocal to date on this issue, but methods are hampered by difficulties in generating and accumulating appropriate particles (especially in the UFP size range) for study. Epidemiological evidence focuses on fine PM; however, the lack of monitoring data for UFPs, issues with measurement technology and the spatial heterogeneity of this size fraction limit the ability of large-scale epidemiologic science to address this issue.

—A subsidiary but important issue involves a better understanding of how effects occur at the biochemical and tissue level. Such work could reveal how individual components of PM exert effects, and to what degree some components are more problematic than others. This would also add to our understanding of how UFPs might be exerting effects, since direct observation of effects is hampered by a variety of factors. Finally, more detailed mechanistic work could enlighten us with regard to whether and by what means chronic exposures alter relevant processes, given the challenges in conducting investigations of chronic morbidity.

- *Chronic effects on progression/instigation of disease*—Studies of chronic effects indicate that PM may be associated with the progression of disease, both cardiac and respiratory. Whether or not this involves the true instigation of disease or is a factor in progression of existing disease is an important uncertainty. Progression of disease is significantly more important than some acute effects, due to the greater public health impact implicit with disease progression. Disease instigation would be an additional step up in the public health impacts of PM. These uncertainties also limit the ability to estimate the life-shortening influence of PM. While this appears to be substantial, and mortality displacement does not seem to be an important aspect of the relationship, only a small number of studies have permitted estimation of life-years lost. Further basic understanding in this area would enhance our abilities to estimate the public health impacts of chronic PM exposure.
- *Variation in severity of pre-existing disease*—The importance of pre-existing disease in understanding the effects of PM, while apparent in some studies, is not entirely clear. Cardiopulmonary disease states are common in Canada (affecting about 40% of the population) and other developed countries. However this large, potentially vulnerable group comprises individuals with a variety of specific disease moieties ranging from quite mild to severe. The influence of both underlying health status and the day-to-day variability in these states appears to be important in understanding PM–health relationships, although many aspects of this have proven difficult to study. Further study in this area is important not only for basic understanding, but also to refine the risk estimates used in regulatory initiatives.
- *Emerging effects of PM*—Although a variety of adverse effects have been associated with PM, mechanistic and toxicological studies of PM indicate that researchers may be missing other significant health endpoints. For example, inflammation is an integral component of most disease processes, which suggests that the inflammatory properties of PM may link it to a much wider range of health outcomes than current evidence would indicate. In addition, there is emerging toxicological evidence of effects beyond the cardiopulmonary systems, including on the CNS and on reproduction and development. Community health studies (e.g. doctors' visits, medication use) are not entirely consistent but indicate the potential for air pollution to affect a broader range of the general public than just those with severe pre-existing disease. Research could serve to elucidate the potential roles of ambient PM in each of these areas, and could support better estimates of the magnitude of the public health impacts of PM.
- *Role of co-pollutants*—The extent to which co-pollutants may modify or contribute to the health effects of PM can also be an important source of uncertainty. Air pollution is a

complex mixture of substances, some of which are often highly correlated with PM, making it difficult to determine the impact of any single pollutant in the mixture. Nonetheless, in those epidemiology studies of mortality or morbidity that included analyses with other pollutants in conjunction with PM, the associations with PM were often fairly robust to adjustment for one or more of ozone, NO₂, SO₂ and CO.

—Toxicological and controlled human exposure studies have also investigated interactions of simple combinations of PM and other pollutants. The evidence for interactive effects is limited and inconclusive, and interactions have generally occurred only at higher than ambient concentrations.

- *Central site monitoring as a measure of exposure*—Exposure analysis studies have answered many of the questions regarding the use of central site monitors to represent population exposure in epidemiological studies. These findings suggest that, although data from central monitors do not reflect the individual variation in personal exposure to PM, they appear to be a reasonable and appropriate measure of population-average exposure to ambient PM. However, bias from exposure misclassification is a concern in any epidemiological analysis. The bias can be either upward or downward, though it is expected to most often underestimate risks and make it more difficult to detect a health effect. Exposure studies have also indicated that while central site monitors work quite well for ambient fine PM, they are not nearly as good for UFPs, PM_{10-2.5}, or many of the components of fine PM. Continued efforts to understand and compensate for these issues are warranted.
- *Concentration–response relationships, thresholds*—For those health endpoints associated with ambient PM in the epidemiological studies, an important question in characterizing risk is the shape of the concentration–response curve, and the issue of potential population threshold levels. Most of the recent studies that have investigated the issue of thresholds continue to show no clear evidence for a threshold in the relationships between PM concentrations and various health endpoints, including premature mortality.

—The lack of a clear threshold at a population level is consistent with the range of susceptibilities to the effects of PM among individuals and between susceptible groups. Although individual thresholds may exist, they are probably widely different, particularly considering that the population-based epidemiological studies include subjects who have the most severe pre-existing disease. In addition, a number of the disease conditions that are affected by PM are common in the general population and have multiple risk factors, in which case PM's contribution would be expected to be incremental, without any evidence of a threshold. However, the extent to which exposure errors, misclassification of exposure, or model specifications may mask potential population thresholds is still not known. Greater clarity on the concentration–response relationship at low concentrations would provide useful information, especially in the realm of benefit–cost analysis, where the absence of a threshold has significant implications.

- *Cumulative risks of short-term exposures*—The majority of epidemiology studies have reported risk estimates for short-term lags, most often for single days. However, the results of some studies have indicated that risks from exposure to PM are greater in relation to longer cumulative periods of several days to month-plus. These findings suggest that for these outcomes the risk estimates reported in epidemiology studies for lags of an individual day or two underestimate the health risks of ambient PM. However, there are also statistical challenges in assessing these data, and while several studies have proposed approaches to examine this phenomenon, additional work could provide additional and complete characterization of these relationships.

14.9.6 Conclusions

This concluding section presents a summary of key findings and insights arising from the preceding sections of the risk characterization for ambient PM. These are presented in point form for various key subject areas, including exposure, the weight of evidence for categories of health effects, subpopulations that are susceptible, and the public health impacts of PM.

- *Exposure*—The entire population is exposed to PM of ambient origin, both when outside and when indoors (since fine PM readily penetrates the building envelope). For epidemiological studies, where estimating population average exposure is required, the ambient monitoring system provides an appropriate representation of exposure to fine PM of ambient origin. In addition, since the ambient and non-ambient components of personal exposure to fine PM appear to be independent, the non-ambient exposure to fine PM is not expected to be a confounder to the effects estimates for PM in epidemiological studies.
- *Acute Respiratory Morbidity and Mortality*—Panel studies demonstrate that current levels of PM_{2.5} are associated with a variety of effects, including reduced lung function, increased respiratory symptoms and pulmonary inflammation. These effects are most pronounced in asthmatic children and adults with COPD, and existing respiratory infections seem to impart greater susceptibility. Work with human volunteers in controlled exposure settings provides some limited support for asthmatics being a sensitive group. Animal toxicology provides support for the lung function effects seen in panel studies, but also important observations related to lung inflammation and injury, providing mechanistic explanations for the effects observed in humans in controlled exposure and epidemiological studies.

—PM-related increases in medical interventions, including doctor's visits, ERVs, and hospital admissions reported in epidemiology studies, are consistent with these effects, especially considering the convergence of the evidence of effects among asthmatic children and persons with COPD, and the appearance of existing respiratory infection as an aggravating factor.

—Thus, based on evidence from several lines of enquiry, the database exhibits strength of association, robustness, consistency, biological plausibility, and coherence. It therefore provides a basis for concluding that there is a **causal relationship** between respiratory morbidity (including decreased lung function, increased respiratory symptoms, and pulmonary inflammation) and acute exposures to PM_{2.5} that results in increased respiratory ERVs and hospitalizations.

—The mechanisms that appear to underlie acute PM morbidity are also applicable to acute exposure mortality. PM appears to increase all-cause and cardiorespiratory mortality, with the identification of those with respiratory infection as being particularly vulnerable; this is consistent with a progression of the inflammatory, cell damage and biochemical mechanisms observed upon acute PM exposure, and the morbidity outcomes described above. Thus, based on several lines of enquiry, the evidence provides a basis for concluding that there is a **causal relationship** between acute exposure to PM_{2.5} and acute respiratory mortality.

- *Chronic Exposure Respiratory Morbidity and Mortality*—In epidemiology studies, long-term exposure to fine ambient PM was associated with adverse respiratory effects, especially in children, including prevalence of chronic bronchitis, reduced lung function growth, and reduced measures of lung function. However, these were often also related to other pollutants, and were not always robust in multi-pollutant models. PM-related increases in otitis media, ear/nose/throat complaints, and wheeze have also been reported, but the database is relatively small and risks were sometimes more strongly related to markers of traffic exposure.

—In laboratory animals, chronic exposure to PM caused hyperplasia and fibrosis in the lung. Though these effects were elicited at high concentrations, they do indicate that PM can induce morphological changes in lungs that could potentially be related to the functional changes observed in the epidemiological studies.

—While the available evidence is **suggestive of a causal relationship** between chronic PM exposure and respiratory morbidity, the possible role of other pollutants and the relatively small number of studies indicates that there is currently inadequate evidence to draw a more definitive conclusion.

—While many studies of premature mortality and chronic exposure to PM have reported significant associations for cardiopulmonary mortality, relatively few have examined respiratory mortality in isolation, and in those that have, the findings have been somewhat inconsistent and not subject to detailed analysis. Thus, current evidence is **inadequate** to draw any conclusions with regard to the causal linkages between chronic exposure to PM and respiratory mortality.

- *Acute Exposure Cardiovascular Morbidity and Mortality*—In population-based epidemiological studies, short-term ambient PM was consistently and significantly associated with increased total and cardiovascular mortality and with cardiovascular hospitalizations and medical visits. Risks for cardiovascular outcomes as a whole were greater than for all-cause, while risks for specific cardiovascular outcomes (ischemic disease (both stroke and cardiac), CHF, and MI) were still greater. Pre-existing cardiorespiratory conditions, especially hypertension, MIs, pneumonia and COPD appeared to confer increased sensitivity for both mortality and hospital visits.

—Such findings are supported by panel studies in which PM was related to increases in biomarkers of vascular coagulation and inflammation, as well as alterations in cardiac function; subjects with hypertension, diabetes and ischaemic conditions were more responsive to PM, especially with respect to measures of cardiac function.

—Animal toxicological experiments provide additional support in the form of clear PM-induced vascular inflammation, thrombosis and vasoreactivity.

—Other pollutants, especially NO₂ but also CO, have been noted to exhibit significant associations with these outcomes as well, and in some cases attenuate (though rarely eliminate) the PM risk association. These co-pollutant associations have been hypothesized to represent particular sources, such as combustion or traffic, though they cannot be ruled out as independent effects. Cardiac function has also been shown to be sensitive to other pollutants, especially NO₂. Generally, though, the association with PM appears consistent.

—Overall, the consistent finding of elevated risk for hospital visits and premature mortality from cardiovascular causes in relation to PM exposure, along with the supporting work from panel and toxicological studies illustrating a range of potential mechanisms in relation to altered and impaired cardiovascular function, exhibits strength of association, robustness, consistency, biological plausibility, and coherence. The database therefore provides a basis for concluding that there is **a causal relationship** between acute exposure to PM_{2.5} and cardiovascular morbidity and mortality

- *Chronic Exposure Cardiovascular Morbidity and Mortality*—In all epidemiological studies of premature mortality in relation to long-term exposure to PM, risks for cardiovascular mortality were greater than those for both all-cause mortality and respiratory mortality, and were still more elevated for IHD, CHF, cardiac arrest and in some cases, for diabetics. Risks were greater for PM_{2.5} than PM₁₀ and were largely independent of other pollutants.

—Studies of cardiovascular morbidity outcomes from chronic PM exposure are rare, but in a recent analysis PM was related to increases in CIMT, a measure of arterial wall thickening associated with atherosclerosis and increased cardiovascular risk.

—The panel and animal study findings of various cardiovascular perturbations provide mechanistic support for these conclusions, though they are largely for acute exposures. Chronic exposure work with compromised laboratory animals and CAPs provides clear mechanistic support for PM-induced atherosclerosis progression, plaque inflammation and instability, as well as compromised cardiac and vascular status.

—The mechanistic findings provide biological plausibility for the effects seen in both the limited morbidity database and the more extensive chronic exposure mortality database. Because the evidence for morbidity is so limited in size and scope, the evidence for cardiovascular morbidity in relation to chronic PM exposure is **suggestive of a causal relationship** at this time. However, based on the consistency of the mortality database, the strong mechanistic support from the findings of the animal toxicological and panel studies, and the general coherence of the database, the evidence for premature cardiovascular mortality indicates that there is **a causal relationship** between chronic exposure to ambient PM_{2.5} and premature cardiovascular mortality

- *Total Mortality*—While this risk characterization has focused on specific respiratory and cardiovascular outcomes, all-cause mortality has been assessed in most studies and until relatively recently was the major outcome grouping evaluated. Given the importance of cardiovascular mortality in overall non-accidental mortality, and the preceding conclusion that chronic exposure to ambient PM is causally related to cardiovascular mortality, it is not surprising that exposure to PM is also consistently associated with all-cause mortality, and it is concluded that there is **a causal relationship** between exposure to ambient PM and total non-accidental mortality. Both acute and chronic exposure mortality studies have been conducted in Canada, or at levels that are consistent with air quality conditions in parts of Canada.

—This all-cause mortality is associated with both acute and chronic exposures to ambient PM; mortality on these two time scales appears to be the result of different but related processes and is concluded to be separate outcomes. Analysis of the ACS and Harvard Six Cities cohorts indicates that chronic exposure advances the date of death of the population by months or years. Acute exposure studies are not as amenable to such analyses; however, examination of the form of the relationship does not indicate that these mortalities are displaced by only a few days (the so-called “harvesting hypothesis”); rather, increased risks are observed over multi-day and month-plus lags and cumulative impacts over these periods are increased compared to single-day maximum risk estimates.

- *Other Effects*—There are important indications from epidemiology studies that lung cancer mortality is associated with long-term exposure to PM. While animal studies done at high exposures provide some mechanistic plausibility for the ability of PM to instigate lung cancer, the epidemiological findings are such that only lung cancer mortality has been evaluated. Though this database is limited, the findings in the strongest studies to date are indicative that there is **likely a causal relationship** with lung cancer mortality.

—Ambient PM has been associated with reproductive and developmental outcomes, including post-natal mortality, preterm birth, IUGR, and LBW in some epidemiological studies. However, associations with other pollutants such as CO and NO₂, as well as with roadway exposure metrics, were often stronger and/or more consistent. Overall, the evidence to date on these outcomes provides evidence that is **suggestive of a causal relationship**.

Nevertheless, additional understanding of the multi-pollutant issue is necessary in order to better understand the implications associated with these outcomes.

- *Subgroups with Increased Sensitivity or Exposure to PM*—Individuals with certain pre-existing diseases appear to be sensitive to exposure to ambient PM. The weight of evidence from controlled human exposure, epidemiological, and animal toxicological studies indicates that asthmatics are a susceptible subgroup. Evidence from epidemiological studies shows that those with COPD are also more susceptible to the effects of PM. A large body of epidemiological and toxicological evidence indicates that people with cardiovascular disease are more susceptible to the health effects of PM. Epidemiology studies have suggested that people with diabetes are also more affected by ambient PM, possibly due to the cardiovascular complications associated with diabetes.

—Age can affect the sensitivity to PM in several respects. The results of epidemiology studies indicate that children, especially asthmatics, may be more at risk of adverse respiratory health outcomes from both acute and chronic PM exposure. Older adults appear to be more sensitive to PM-related effects, especially cardiovascular outcomes including mortality, perhaps as a result of the high prevalence of cardiovascular diseases in this age group.

—Some subgroups have greater exposures to and are more affected by PM. There is evidence that these include children spending more time outdoors, populations in which there is less use of residential air conditioning (and hence greater infiltration of ambient PM), exercising individuals, and populations that reside near major roadways. The latter source may also in part account for a number of reports that PM risks are greater in populations with lower socioeconomic status.

- *Public Health Impacts*—The effects associated with PM have been observed in epidemiological studies in Canada, as well as in epidemiological studies in other countries with PM concentrations that occur in Canada.

—In most of the studies that examined the shape of the concentration–response relationship for PM-related mortality (both acute and chronic) or hospitalizations, there was an approximately linear relationship, with no clear evidence for a threshold. The lack of a population threshold is consistent with the range of susceptibilities to the effects of PM among individuals and between susceptible groups within the general population, and with the high prevalence and multi-factorial nature of a number of the disease conditions that are associated with PM. While there are limitations in the ability of epidemiological methods to determine the presence or absence of thresholds of effect, well-conducted studies examining this phenomenon have concluded that population effect thresholds, should they exist, would be at very low ambient concentrations. Consequently, the available evidence indicates that any increment in anthropogenic concentrations of ambient fine PM presents an increased risk for serious health effects, including premature mortality.

—Although the risks for PM-related health effects are relatively small by traditional epidemiological standards, the entire population is exposed to ambient PM, and the subpopulations that have increased sensitivity or exposure to PM (including older adults, children, and individuals with certain common conditions (asthma, COPD, cardiovascular diseases)) comprise a considerable proportion of the population. In addition, the serious health impacts that have been the focus of most assessments, including mortality, hospitalizations, and ERVs are just the “tip of the iceberg” in the pyramid of health effects associated with PM, and the unmeasured morbidity has important public health impacts and costs. As a result, the public health effects of ambient PM are substantial, and they can only

be expected to grow as the population ages and the prevalence of age-related diseases that confer susceptibility to PM increases.

14.10 References

- Abadie M, Limam K, Bouilly J, and Genin D. 2004. Particle pollution in the French high-speed train (TGV) smoker cars: measurement and prediction of passengers exposure. *Atmos Env* 38:2017–27.
- Abrahamowicz M, Schopflocher T, Leffondre K, du Berger R, and Krewski D. 2003. Flexible modeling of exposure–response relationship between long-term average levels of particulate air pollution and mortality in the American Cancer Society study. *J Tox Environ Health A* 66:1625–54.
- Abt E, Suh HH, Allen G, and Koutrakis P. 2000a. Characterization of indoor particle sources: A study conducted in the metropolitan Boston area. *Environ Health Perspect* 108:35–44.
- Abt E, Suh HH, Catalano P, and Koutrakis P. 2000b. Relative contribution of outdoor and indoor particle sources to indoor concentrations. *Environ Sci Technol* 34:3579–87.
- Adamkiewicz G, Ebelt S, Syring M, Slater J, Speizer FE, Schwartz J, Suh H, and Gold DR. 2004. Association between air pollution exposure and exhaled nitric oxide in an elderly population. *Thorax* 59:204–9.
- Adams HS, Kenny LC, Nieuwenhuijsen MJ, Colvile RN, and Gussman RA. 2001a. Design and validation of a high-flow personal sampler for PM_{2.5}. *J Expo Analysis Environ Epidemiol* 11:5–11.
- Adams HS, Nieuwenhuijsen MJ, Colvile RN, McMullen MAS, and Khandelwal P. 2001b. Fine particle (PM_{2.5}) personal exposure levels in transport microenvironments, London, UK. *Sci Total Env* 279:29–44.
- Adgate JL, Ramachandran G, Pratt GC, Waller LA, and Sexton K. 2003. Longitudinal variability in outdoor, indoor, and personal PM_{2.5} exposure in healthy non-smoking adults. *Atmos Env* 37:993–1002.
- Aekplakorn W, Loomis D, Vichit-Vadakan N, Shy C, Wongtim S, and Vitayanon P. 2003a. Acute effect of sulphur dioxide from a power plant on pulmonary function of children, Thailand. *Int J Epidemiol* 32:854–61.
- Aekplakorn W, Loomis D, Vichit-Vadakan N, Shy C, and Plungchuchon S. 2003b. Acute effects of SO₂ and particles from a power plant on respiratory symptoms of children, Thailand. *Southeast Asian J Trop Med Public Health* 34:906–14.
- Aga E, Samoli E, Touloumi G, Anderson HR, Cadum E, Forsberg B, Goodman P, Goren A, Kotesovec F, Kriz B, Macarol-Hiti M, Medina S, Paldy A, Schindler C, Sunyer J, Tittanen P, Wojtyniak B, Zmirou D, Schwartz J, and Katsouyanni K. 2003. Short-term effects of ambient particles on mortality in the elderly: results from 28 cities in the APHEA2 project. *Eur Respir J Suppl* 40:28s–33s.
- Agopyan N, Bhatti T, Yu S, and Simon SA. 2003a. Vanilloid receptor activation by 2- and 10-microm particles induces responses leading to apoptosis in human airway epithelial cells. *Toxicol Appl Pharmacol* 192:21–35.
- Agopyan N, Li L, Yu S, and Simon SA. 2003b. Negatively charged 2- and 10-microm particles activate vanilloid receptors, increase cAMP, and induce cytokine release. *Toxicol Appl Pharmacol* 186:63–76.
- Agopyan N, Head J, Yu S, and Simon SA. 2004. TRPV1 receptors mediate particulate matter-induced apoptosis. *Am J Physiol Lung Cell Mol Physiol* 286:L563–72.

- Agranovski IE, Braddock D, and Myojo T. 1999. Removal of aerosols by bubbling through porous media. *Aerosol Sci Tech* 31:249–57.
- Agranovsky IE, Braddock D, and Myojo T. 2001. Comparative study of the performance of nine filters utilized in filtration of aerosols by bubbling. *Aerosol Sci Tech* 35:852–9.
- Agranovski IE, Huang R, Pyankov OV, Altman IS, and Grinshpun SA. 2006. Enhancement of the performance of low-efficiency HVAC filters due to continuous unipolar ion emission. *Aerosol Sci Tech* 40:963–8.
- Alessandrini F, Schulz H, Takenaka S, Lentner B, Karg E, Behrendt H, and Jakob T. 2006. Effects of ultrafine carbon particle inhalation on allergic inflammation of the lung. *J Allergy Clin Immunol* 117:824–30.
- Allen R, Larson T, Sheppard L, Wallace L, and Liu LJS. 2003. Use of real-time light scattering data to estimate the contribution of infiltrated and indoor-generated particles to indoor air. *Environ Sci Technol* 37:3484–92.
- Allen R, Wallace L, Larson T, Sheppard L, and Liu LJS. 2004. Estimated hourly personal exposures to ambient and nonambient particulate matter among sensitive populations in Seattle, Washington. *J Air Waste Man Assoc* 54:1197–1211.
- Alves CA and Ferraz CA. 2005. Effects of air pollution on emergency admissions for chronic obstructive pulmonary diseases in Oporto, Portugal. *Int J Env Pollut* 23:42–64.
- Analitis AKK, Dimakopoulou K, Samoli E, Nikoloulopoulos AK, Petasakis Y, Touloumi G, Schwartz J, Anderson HR, Cambra K, Forastiere F, Zmirou D, Vonk JM, Clancy L, Kriz B, André E, Stoeger T, Takenaka S, Bahnweg M, Ritter B, Karg E, Lentner B, Reinhard C, Schulz H, and Wjst M. 2006. Inhalation of ultrafine carbon particles triggers biphasic pro-inflammatory response in the mouse lung. *Eur Respir J* 28:275–85.
- Anderson HR, Atkinson A, Peacock JL, Sweeting MJ and Marston L. 2005. Ambient Particulate matter and health effects: Publication bias in studies of short-term associations. *Epidemiology* 16:155–163.
- André E, Stoeger T, Takenaka S, Bahnweg M, Ritter B, Karg E, Lentner B, Reinhard C, Schulz H, and Wjst M. 2006. Inhalation of ultrafine carbon particles triggers biphasic pro-inflammatory response in the mouse lung. *Eur Respir J* 28:275–85.
- Antonini JM, Taylor MD, Leonard SS, Lawryk NJ, Shi X, Clarke RW, and Roberts JR. 2004. Metal composition and solubility determine lung toxicity induced by residual oil fly ash collected from different sites within a power plant. *Mol Cell Biochem* 255:257–65.
- Archer AJ, Cramton JL, Pfau JC, Colasurdo G, and Holian A. 2004. Airway responsiveness after acute exposure to urban particulate matter 1648 in a DO11.10 murine model. *Am J Physiol Lung Cell Mol Physiol* 286:L337–43.
- Arena VC, Mazumdar S, Zborowski JV, Talbott EO, He S, Chuang YH, and Schwerha JJ. 2006. A retrospective investigation of PM₁₀ in ambient air and cardiopulmonary hospital admissions in Allegheny County, Pennsylvania: 1995–2000. *J Occup Environ Med* 48:38–47.
- Asgharian B and Price OT. 2004. Models of airflow transport in the human lung. *Adv Bioeng*:21–2.
- Asgharian B, Hofmann W, and Miller FJ. 2006. Dosimetry of Particles in Humans: From Children to Adults. *In: Toxicology of the Lung, Fourth Ed.* Taylor and Francis Group, CRC Press. ISBN: 0-8493-2835-7

- Aust AE, Ball JC, Hu AA, Lighty JS, Smith KR, Straccia AM, Veranth JM, and Young WC. 2002. Particle characteristics responsible for effects on human lung epithelial cells. *Res Rep Health Eff Inst* 110:1–76.
- Avol EL, Gauderman WJ, Tan SM, London SJ, and Peters JM. 2001. Respiratory effects of relocating to areas of differing air pollution levels. *Am J Respir Crit Care* 164:2067–2072.
- Bagate K, Meiring JJ, Cassee FR, and Borm PJ. 2004a. The effect of particulate matter on resistance and conductance vessels in the rat. *Inhal Toxicol* 16:431–6.
- Bagate K, Meiring JJ, Gerlofs-Nijland ME, Vincent R, Cassee FR, and Borm PJ. 2004b. Vascular effects of ambient particulate matter instillation in spontaneous hypertensive rats. *Toxicol Appl Pharmacol* 197:29–39.
- Bagate K, Meiring JJ, Gerlofs-Nijland ME, Cassee FR, and Borm PJ. 2006a. Signal transduction pathways involved in particulate matter induced relaxation in rat aorta--spontaneous hypertensive versus Wistar Kyoto rats. *Toxicol in Vitro* 20:52–62.
- Bagate K, Meiring JJ, Gerlofs-Nijland ME, Cassee FR, Wiegand H, Osornio-Vargas A, and Borm PJ. 2006b. Ambient particulate matter affects cardiac recovery in a Langendorff ischemia model. *Inhal Toxicol* 18:633–43.
- Bahadori T. 1998. Personal exposure to particulate matter of individuals with chronic obstructive pulmonary disease (COPD). *In* Human particulate exposure assessment: relationship between outdoor, indoor and personal measurements. Ph.D. Thesis. Boston, MA: Harvard School of Public Health.
- Bakonyi SM, Danni-Oliveira IM, Martins LC, and Braga AL. 2004. [Air pollution and respiratory diseases among children in the city of Curitiba, Brazil]. *Rev Saude Publica* 38:695–700.
- Ballester F, Saez M, Perez-Hoyos S, Iniguez C, Gandarillas A, Tobias A, Bellido J, Taracido M, Arribas F, Daponte A, Alonso E, Canada A, Guillen-Grima F, Cirera L, Perez-Boillos MJ, Saurina C, Gomez F, and Tenias JM. 2002. The EMECAM project: a multicentre study on air pollution and mortality in Spain: combined results for particulates and for sulfur dioxide. *Occup Environ Med* 59:300–8.
- Ballester F, Rodriguez P, Iniguez C, Saez M, Daponte A, Galan I, Taracido M, Arribas F, Bellido J, Cirarda FB, Canada A, Guillen JJ, Guillen-Grima F, Lopez E, Perez-Hoyos S, Lertxundi A, and Toro S. 2006. Air pollution and cardiovascular admissions association in Spain: results within the EMECAS project. *J Epidemiol Community Health* 60:328–336.
- Barlow PG, Clouter-Baker A, Donaldson K, Maccallum J, and Stone V. 2005. Carbon black nanoparticles induce type II epithelial cells to release chemotaxins for alveolar macrophages. *Part Fibre Toxicol* 2:11–24.
- Barnett AG, Williams GM, Schwartz J, Neller AH, Best TL, Petroeschevsky AL, and Simpson RW. 2005. Air pollution and child respiratory health: a case-crossover study in Australia and New Zealand. *Am J Respir Crit Care Med* 171:1272–8.
- Barrett EG, Rudolph K, Bowen LE, Muggenburg BA, and Bice DE. 2003. Effect of inhaled ultrafine carbon particles on the allergic airway response in ragweed-sensitized dogs. *Inhal Toxicol* 15:151–65.
- Basu R, Woodruff TJ, Parker JD, Saulnier L, and Schoendorf KC. 2004. Comparing exposure metrics in the relationship between PM_{2.5} and birth weight in California. *J Expo Anal Environ Epidemiol* 14:391–6.

- Batalha JR, Saldiva PH, Clarke RW, Coull BA, Stearns RC, Lawrence J, Murthy GG, Koutrakis P, and Godleski JJ. 2002. Concentrated ambient air particles induce vasoconstriction of small pulmonary arteries in rats. *Environ Health Perspect* 110:1191–7.
- Bateson TF and Schwartz J. 2004. Who is sensitive to the effects of particulate air pollution on mortality? A case-crossover analysis of effect modifiers. *Epidemiology* 15:143–9.
- Batterman S, Godwin C, and Jia C. 2005. Long duration tests of room air filters in cigarette smokers' homes. *Environ Sci Technol* 39:7260–8.
- Bayer-Oglesby L, Grize L, Gassner M, Takken-Sahli K, Sennhauser FH, Neu U, Schindler C, and Braun-Fahrlander C. 2005. Decline of ambient air pollution levels and improved respiratory health in Swiss children. *Environ Health Perspect* 113:1632–7.
- Becker S and Soukup J. 2003. Coarse (PM(2.5–10)), fine (PM(2.5)), and ultrafine air pollution particles induce/increase immune costimulatory receptors on human blood-derived monocytes but not on alveolar macrophages. *J Toxicol Environ Health A* 66:847–59.
- Becker S, Soukup JM, Sioutas C, and Cassee FR. 2003. Response of human alveolar macrophages to ultrafine, fine, and coarse urban air pollution particles. *Exp Lung Res* 29:29–44.
- Becker S, Dailey LA, Soukup JM, Grambow SC, Devlin RB, and Huang YC. 2005a. Seasonal variations in air pollution particle-induced inflammatory mediator release and oxidative stress. *Environ Health Perspect* 113:1032–8.
- Becker S, Mundandhara S, Devlin RB, and Madden M. 2005b. Regulation of cytokine production in human alveolar macrophages and airway epithelial cells in response to ambient air pollution particles: Further mechanistic studies. *Toxicol Appl Pharmacol* 207:S269–75.
- Beckett WS, Chalupa DF, Pauly-Brown A, Speers DM, Stewart JC, Frampton MW, Utell MJ, Huang LS, Cox C, Zareba W, and Oberdörster G. 2005. Comparing inhaled ultrafine versus fine zinc oxide particles in healthy adults: a human inhalation study. *Am J Respir Crit Care Med* 171:1129–35.
- Beck-Speier I, Dayal N, Karg E, Maier KL, Schulz H, Schumann G, Ziesenis A, and Heyder J. 2003. Formation of prostaglandin E₂, leukotriene B₄ and 8-isoprostane in alveolar macrophages by ultrafine particles of elemental carbon. *Adv Exp Med Biol* 525:117–20.
- Beck-Speier I, Dayal N, Karg E, Maier KL, Schumann G, Schulz H, Semmler M, Takenaka S, Stettmaier K, Bors W, Ghio A, Samet JM, and Heyder J. 2005. Oxidative stress and lipid mediators induced in alveolar macrophages by ultrafine particles. *Free Radic Biol Med* 38:1080–92.
- Bennett WD and Zeman KL. 2004. Effect of body size on breathing pattern and fine-particle deposition in children. *J Appl Physiol* 97:821–6.
- Berger A, Zareba W, Schneider A, Ruckerl R, Ibaldo-Mulli A, Cyrys J, Wichmann HE, and Peters A. 2006. Runs of ventricular and supraventricular tachycardia triggered by air pollution in patients with coronary heart disease. *J Occup Environ Med* 48:1149–58.
- Berktaş BM and Bircan A. 2003. Effects of atmospheric sulphur dioxide and particulate matter concentrations on emergency room admissions due to asthma in Ankara. *Tuberk Toraks* 51:231–8.
- Bermudez E, Mangum JB, Wong BA, Asgharian B, Hext PM, Warheit DB, and Everitt JI. 2004. Pulmonary responses of mice, rats, and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. *Toxicol Sci* 77:347–57.

- Biggeri A, Baccini M, Bellini P, and Terracini B. 2005. Meta-analysis of the Italian studies of short-term effects of air pollution (MISA), 1990–1999. *Int J Occup Environ Health* 11:107–22.
- Binková B, Lewtas J, Mišková I, Leniček J, and Šrám R. 1995. DNA adducts and personal air monitoring of carcinogenic polycyclic aromatic hydrocarbons in an environmentally exposed population. *Carcinogenesis* 16:1037–46.
- Binková B, Cerna M, Pastorkova A, Jelinek R, Benes I, Novak J, and Sram RJ. 2003. Biological activities of organic compounds adsorbed onto ambient air particles: comparison between the cities of Teplice and Prague during the summer and winter seasons 2000–2001. *Mutat Res* 525:43–59.
- Bitterle E, Karg E, Schroepel A, Kreyling WG, Tippe A, Ferron GA, Schmid O, Heyder J, Maier KL, and Hofer T. 2006. Dose-controlled exposure of A549 epithelial cells at the air–liquid interface to airborne ultrafine carbonaceous particles. *Chemosphere* 65:1784–90.
- Bobvos J, and Pekkanen J. 2006. Short-term effects of ambient particles on cardiovascular and respiratory mortality. *Epidemiology* 17:230–3.
- Boezen HM, Vonk JM, van der Zee SC, Gerritsen J, Hoek G, Brunekreef B, Schouten JP, and Postma DS. 2005. Susceptibility to air pollution in elderly males and females. *Eur Respir J* 25:1018–24.
- Bogdanovic D, Nikic DS, Milosevic ZG, and Stankovic AM. 2006. Black smoke air pollution and daily non-accidental mortality in Nis, Serbia. *Cent Eur J Med* 1:292–7.
- Borm PJ, Cakmak G, Jermann E, Weishaupt C, Kempers P, van Schooten FJ, Oberdörster G, and Schins RP. 2005. Formation of PAH-DNA adducts after *in vivo* and *in vitro* exposure of rats and lung cells to different commercial carbon blacks. *Toxicol Appl Pharmacol* 205:157–67.
- Boudet C, Zmirou D, and Dechenaux J. 2000. [Personal exposure to fine particles (PM_{2.5}) in the Grenoble population: European EXPOLIS study]. *Rev Epidemiol Sante* 48:341–50.
- Bourcier T, Viboud C, Cohen J-C, Thomas F, Bury T, Cadiot L, Mestre O, Flahaut A, Borderie V, and Laroche L. 2003. Effects of air pollution and climatic conditions on the frequency of ophthalmological emergency examinations. *Br J Ophthalmol* 87:809–11.
- Bowser D. 1999. Evaluation of residential furnace filters. Ottawa, ON: Canada Mortgage and Housing Corporation. Housing Technology Series. Research Report No. 61607. Cat. No. NH15-318/1999E.
- Brauer M, Koutrakis P, and Spengler, JD. 1989. Personal exposures to acidic aerosols and gases. *Environ Sci Technol* 23:1408–12.
- Brauer M, Koutrakis P, Keeler GJ, and Spengler JD. 1990. Indoor and outdoor concentrations of acidic aerosols and gases. In: *Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, volume 2, characteristics of indoor air; July–August; Toronto, ON, Canada*. Ottawa, ON, Canada: International Conference on Indoor Air Quality and Climate, Inc: 447–52.
- Brauer M, Koutrakis P, Keeler GJ, and Spengler JD. 1991. Indoor and outdoor concentrations of inorganic acidic aerosols and gases. *J Air Waste Man Assoc* 41:171–81.
- Brauer M, Hrubá F, Mihalíková E, Fabiánová E, Miskovic P, Plžiková A, Lendacká M, Vandenberg J, and Cullen A. 2000. Personal exposure to particles in Banská Bystrica, Slovakia. *J Expo Analysis Environ Epidemiol* 10:478–87.

- Brauer M, Hoek G, Van Vliet P, Meliefste K, Fischer PH, Wijga A, Koopman LP, Neijens HJ, Gerritsen J, Kerkhof M, Heinrich J, Bellander T, and Brunekreef B. 2002. Air pollution from traffic and the development of respiratory infections and asthmatic and allergic symptoms in children. *Am J Respir Crit Care Med* 166:1092–8.
- Brauer M, Gehring U, Brunekreef B, De Jongste J, Gerritsen J, Rovers M, Wichmann HE, Wijga A, and Heinrich J. 2006. Traffic-related air pollution and otitis media. *Environ Health Perspect* 114:1414–18.
- Braun-Fahrlander C, Vuille JC, Sennhauser FH, Neu U, Kunzle T, Grize L, Gassner M, Minder C, Schindler C, Varonier HS, and Wuthrich B. 1997. Respiratory health and long-term exposure to air pollutants in Swiss schoolchildren. *Am J Respir Crit Care Med* 155:1042–9.
- Brinkman G, Vance G, Hannigan MP, and Milford JB. 2006. Use of synthetic data to evaluate positive matrix factorization as a source apportionment tool for PM_{2.5} exposure data. *Environ Sci Technol* 40:1892–1901.
- Brits E, Schoeters G, and Verschaeve L. 2004. Genotoxicity of PM₁₀ and extracted organics collected in an industrial, urban and rural area in Flanders, Belgium. *Environ Res* 96:109–18.
- Brodsky DM. 2004. Deposition of ultrafine particles at carinal ridges of the upper bronchial airways. *Aerosol Sci Technol* 38:991–1000.
- Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, and Silverman F. 2002. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation* 105:1534–6.
- Brook RD, Franklin B, Cascio W, Hong Y, Howard G, Lipsett M, Luepker R, Mittleman M, Samet J, Smith SC Jr, and Tager I. 2004. Air pollution and cardiovascular disease: a statement for healthcare professionals from the Expert Panel on Population and Prevention Science of the American Heart Association. *Circulation* 109:2655–71.
- Brown DM, Donaldson K, Borm PJ, Schins RP, Dehnhardt M, Gilmour P, Jimenez LA, and Stone V. 2004a. Calcium and ROS-mediated activation of transcription factors and TNF-alpha cytokine gene expression in macrophages exposed to ultrafine particles. *Am J Physiol Lung Cell Mol Physiol* 286:L344–53.
- Brown DM, Donaldson K, and Stone V. 2004b. Effects of PM₁₀ in human peripheral blood monocytes and J774 macrophages. *Respir Res* 5:29–40.
- Brown JS, Wilson WE, and Grant LD. 2005. Dosimetric comparisons of particle deposition and retention in rats and humans. *Inhal Toxicol* 17:355–85.
- Brunekreef B, Janssen NAH, de Hartog JJ, Oldenwening M, Meliefste K, Hoek G, Lanki T, Timonen KL, Vallius M, Pekkanen J, and Van Grieken R. 2005. Personal, indoor, and outdoor exposures to PM_{2.5} and its components for groups of cardiovascular patients in Amsterdam and Helsinki. Boston, MA: Health Effects Institute. Research Report No.127.
- Burke J, Zufall MJ, and Özkaynak H. 2001. A population exposure model for particulate matter: case study results for PM_{2.5} in Philadelphia, PA. *J Expo Analysis Environ Epidemiol* 11:470–89.
- Burnett RT, Stieb D, Brook JR, Cakmak S, Dales R, Raizenne M, Vincent R, and Dann T. 2004. Associations between short-term changes in nitrogen dioxide and mortality in Canadian cities. *Arch Environ Health* 59:228–36.
- Burr ML, Karani G, Davies B, Holmes BA, and Williams KL. 2004. Effects on respiratory health of a reduction in air pollution from vehicle exhaust emissions. *Occup Environ Med* 61:212–18.

- Calcabrini A, Meschini S, Marra M, Falzano L, Colone M, De Berardis B, Paoletti L, Arancia G, and Fiorentini C. 2004. Fine environmental particulate engenders alterations in human lung epithelial A549 cells. *Environ Res* 95:82–91.
- Campbell A. 2004. Inflammation, neurodegenerative diseases, and environmental exposures. *Ann N Y Acad Sci* 1035:117–32.
- Campbell A, Oldham M, Becaria A, Bondy SC, Meacher D, Sioutas C, Misra C, Mendez LB, and Kleinman M. 2005. Particulate matter in polluted air may increase biomarkers of inflammation in mouse brain. *Neurotoxicology* 26:133–40.
- Campen MJ, McDonald JD, Reed MD, and Seagrave J. 2006. Fresh gasoline emissions, not paved road dust, alter cardiac repolarization in ApoE^{-/-} mice. *Cardiovasc Toxicol* 6:199–210.
- Canadian Council of Ministers of the Environment. Guidance Document on Achievement Determination, Canada-wide Standards for Particulate Matter and Ozone. 2007. Winnipeg, Manitoba: Canadian Council of Ministers of the Environment. PN 1391 978-1-896997-74-2 PDF.
- Cançado JED, Saldiva PHN, Pereira LAA, Lara LBL, Artaxo P, Martinelli LA, Arbex MA, Zanobetti A, and Braga ALF. 2006. The impact of sugar cane-burning emissions on the respiratory system of children and the elderly. *Environ Health Perspect* 114:725–9.
- Cao JJ, Lee SC, Chow JC, Cheng Y, Ho KF, Fung K, Liu SX, and Watson JG. 2005. Indoor/outdoor relationships for PM_{2.5} and associated carbonaceous pollutants at residential homes in Hong Kong—case study. *Indoor Air* 15:197–204.
- Carrothers TJ and Evans JS. 2000. Assessing the impact of differential measurement error on estimates of fine particle mortality. *J Air Waste Man Assoc* 50:65–74.
- Carter JM, Corson N, Driscoll KE, Elder A, Finkelstein JN, Harkema JN, Gelein R, Wade-Mercer P, Nguyen K, and Oberdörster G. 2006. A comparative dose-related response of several key pro- and antiinflammatory mediators in the lungs of rats, mice, and hamsters after subchronic inhalation of carbon black. *J Occup Environ Med* 48:1265–78.
- Cassee F, Fokkens P, Leseman D, Bloemen H, and Boere A. 2003. Respiratory Allergy and Inflammation Due to Ambient Particles (RAIAP): Collection of Particulate Matter samples from 5 European sites with High Volume Cascade Impactors. Rijksinstituut voor Volksgezondheid en Milieu (RIVM) Report # 863001001:1–62.
- Cassee FR, Boere AJ, Fokkens PH, Leseman DL, Sioutas C, Kooter IM, and Dormans JA. 2005. Inhalation of concentrated particulate matter produces pulmonary inflammation and systemic biological effects in compromised rats. *J Toxicol Environ Health A* 68:773–96.
- Center for Health Research (CIIT). 2005. Technology Transfer. <http://www.ciit.org/mpppd/>
- Chalupa DC, Morrow PE, Oberdörster G, Utell MJ, and Frampton MW. 2004. Ultrafine particle deposition in subjects with asthma. *Environ Health Perspect* 112:879–82.
- Chan AT. 2002. Indoor–outdoor relationships of particulate matter and nitrogen oxides under different outdoor meteorological conditions. *Atmos Env* 36:1543–51.
- Chan CC and Wu TH. 2005. Effects of ambient ozone exposure on mail carriers' peak expiratory flow rates. *Environ Health Perspect* 113:735–8.
- Chan CC, Chuang KJ, Shiao GM, and Lin LY. 2004. Personal exposure to submicrometer particles and heart rate variability in human subjects. *Environ Health Perspect* 112:1063–7.
- Chan CC, Chuang KJ, Su TC, and Lin LY. 2005. Association between nitrogen dioxide and heart rate variability in a susceptible population. *Eur J Cardiovasc Prev Rehabil* 12:580–6.

- Chan CC, Chuang KJ, Chien LC, Chen WJ, and Chang WT. 2006. Urban air pollution and emergency admissions for cerebrovascular diseases in Taipei, Taiwan. *Eur Heart J* 27:1238-1244.
- Chang CC, Hwang JS, Chan CC, Wang PY, Hu TH, and Cheng TJ. 2004. Effects of concentrated ambient particles on heart rate, blood pressure, and cardiac contractility in spontaneously hypertensive rats. *Inhal Toxicol* 16:421-9.
- Chang CC, Tsai SS, Ho SC, and Yang CY. 2005a. Air pollution and hospital admissions for cardiovascular disease in Taipei, Taiwan. *Environ Res* 98:114-19.
- Chang CC, Chiu HF, Wu YS, Li YC, Tsai ML, Shen CK, and Yang CY. 2005b. The induction of vascular endothelial growth factor by ultrafine carbon black contributes to the increase of alveolar-capillary permeability. *Environ Health Perspect* 113:454-60.
- Chang CC, Lee IM, Tsai SS, and Yang CY. 2006. Correlation of Asian dust storm events with daily clinic visits for allergic rhinitis in Taipei, Taiwan. *J Toxicol Environ Health A* 69:229-35.
- Chao CYH, Wan MP, and Cheng ECK. 2003. Penetration coefficient and deposition rate as a function of particle size in non-smoking naturally ventilated residences. *Atmos Env* 37:4233-41.
- Chardon B, Lefranc A, Granados D, and Gremy I. 2007. Air pollution and doctors' house calls for respiratory diseases in Greater Paris area (2000-2003). *Occup Environ Med* 64:320-324 (pre-published online in 2006).
- Chauhan V, Breznan D, Goegan P, Nadeau D, Karthikeyan S, Brook JR, and Vincent R. 2004. Effects of ambient air particles on nitric oxide production in macrophage cell lines. *Cell Biol Toxicol* 20:221-39.
- Chauhan V, Breznan D, Thomson E, Karthikeyan S, and Vincent R. 2005. Effects of ambient air particles on the endothelin system in human pulmonary epithelial cells (A549). *Cell Biol Toxicol* 21:191-205.
- Chen C-C. Performance comparison of indoor air cleaners. 2006. *In Proceedings of the AWMA Indoor Environmental Quality: Problems, Research and Solutions Conference*. Durham, North Carolina, July, 2006. 109.
- Chen L, Verrall K, and Tong S. 2006. Air particulate pollution due to bushfires and respiratory hospital admissions in Brisbane, Australia. *Int J Environ Health Res* 16:181-91.
- Chen LC and Hwang JS. 2005. Effects of subchronic exposures to concentrated ambient particles (CAPs) in mice. IV. Characterization of acute and chronic effects of ambient air fine particulate matter exposures on heart-rate variability. *Inhal Toxicol* 17:209-16.
- Chen LC and Nadziejko C. 2005. Effects of subchronic exposures to concentrated ambient particles (CAPs) in mice. V. CAPs exacerbate aortic plaque development in hyperlipidemic mice. *Inhal Toxicol* 17:217-24.
- Chen LH, Knutsen SF, Shavlik D, Beeson WL, Petersen F, and Ghamsary M. 2005a. The association between fatal coronary heart disease and ambient particulate air pollution: Are females at greater risk? *Environ Health Perspect* 113:1723-9.
- Chen Y, Yang Q, Krewski D, Burnett RT, Shi Y, and McGrail KM. 2005b. The effect of coarse ambient particulate matter on first, second, and overall hospital admissions for respiratory disease among the elderly. *Inhal Toxicol* 17:649-55.
- Chen YS, Sheen PC, Chen ER, Liu YK, Wu TN, and Yang CY. 2004a. Effects of Asian dust storm events on daily mortality in Taipei, Taiwan. *Environ Res* 95:151-5.

- Chen Y, Yang Q, Krewski D, Shi Y, Burnett RT, and McGrail K. 2004b. Influence of relatively low level of particulate air pollution on hospitalization for COPD in elderly people. *Inhal Toxicol* 16:21–5.
- Cheng MD. 2004. Effects of nanophase materials (< or = 20 nm) on biological responses. *J Environ Sci Health A Tox Hazard Subst Environ Eng* 39:2691–705.
- Chillrud SN, Epstein D, Ross JM, Sax SN, Pederson D, Spengler JD, and Kinney PL. 2004. Elevated airborne exposures of teenagers to manganese, chromium, and iron from steel dust and New York City's subway system. *Environ Sci Technol* 38:732–7.
- Cho AK, Sioutas C, Miguel AH, Kumagai Y, Schmitz DA, Singh M, Eiguren-Fernandez A, and Froines JR. 2005a. Redox activity of airborne particulate matter at different sites in the Los Angeles Basin. *Environ Res* 99:40–7.
- Cho HY, Jedlicka AE, Clarke R, and Kleeberger SR. 2005b. Role of Toll-like receptor-4 in genetic susceptibility to lung injury induced by residual oil fly ash. *Physiol Genomics* 22:108–17.
- Chow JC and Watson JG. 2002. Review of PM_{2.5} and PM₁₀ apportionment for fossil fuel combustion and other sources by the chemical mass balance receptor model. *Energ Fuel* 16: 222–60.
- Chow JC, Watson JG, Pritchett LC, Pierson WR, Frazier CA, and Purcell RG. 1993. The DRI thermal/optical reflectance carbon analysis system: description, evaluation and applications in U.S. air quality studies. *Atmos Env A* 27:1185–1201.
- Chow JC, Watson JG, Crow D, Lowenthal DH, and Merrifield T. 2001. Comparison of IMPROVE and NIOSH carbon measurements. *Aerosol Sci Tech* 34:23–34.
- Chuang KJ, Chan CC, Chen NT, Su TC, and Lin LY. 2005a. Effects of particle size fractions on reducing heart rate variability in cardiac and hypertensive patients. *Environ Health Perspect* 113:1693–7.
- Chuang KJ, Chan CC, Shiao GM, and Su TC. 2005b. Associations between submicrometer particles exposures and blood pressure and heart rate in patients with lung function impairments. *J Occup Environ Med* 47:1093–8.
- Churg A, Xie C, Wang X, Vincent R, and Wang RD. 2005. Air pollution particles activate NF-kappaB on contact with airway epithelial cell surfaces. *Toxicol Appl Pharmacol* 208:37–45.
- Clancy L, Goodman P, Sinclair H, and Dockery DW. 2002. Effect of air-pollution control on death rates in Dublin, Ireland: an intervention study. *The Lancet* 360:1210–14.
- Clayton CA, Perritt RL, Pellizzari ED, Thomas KW, Whitmore RW, Wallace LA, Özkaynak H, and Spengler JD. 1993. Particle total exposure assessment methodology (PTEAM) study: distribution of aerosol and elemental concentrations in personal, indoor and outdoor air samples in a Southern California community. *J Expo Analysis Environ Epidemiol* 3:227–50.
- Clayton CA, Pellizzari ED, Rodes CE, Mason RE, and Pipier LL. 1999. Estimating distributions of long-term particulate matter and manganese exposures for residents of Toronto, Canada. *Atmos Env* 33:2515–26.
- Colome SD, Kado NY, Jaques P, and Kleinman M. 1992. Indoor–outdoor air pollution relations: particulate matter less than 10 microns in aerodynamic diameter (PM₁₀) in homes of asthmatics. *Atmos Env A* 26:2173–8.
- Corcoran TE, Chigier NA, Allen GM, Shorthall BP, and Gemci T. 2004. Computational simulations of airflow in an *in vitro* model of the pediatric upper airways. *J Biomech Eng* 106:604–13.

- Costa DL and Kodavanti UP. 2003. Toxic responses of the lung to inhaled pollutants: benefits and limitations of lung-disease models. *Toxicol Lett* 140–141:195–203.
- Costa DL, Lehmann JR, Winsett D, Richards J, Ledbetter AD, and Dreher KL. 2006. Comparative pulmonary toxicological assessment of oil combustion particles following inhalation or instillation exposure. *Toxicol Sci* 91:237–46.
- Cozzi E, Hazarika S, Stallings HW 3rd, Cascio WE, Devlin RB, Lust RM, Wingard CJ, and Van Scott MR. 2006. Ultrafine particulate matter exposure augments ischemia-reperfusion injury in mice. *Am J Physiol Heart Circ Physiol* 291:H894–903.
- Crump KS. 2000. Manganese exposures in Toronto during use of the gasoline additive, methylcyclopentadienyl manganese tricarbonyl. *J Expo Analysis Environ Epidemiol* 10:227–39.
- Cyrys J, Heinrich J, Hoek G, Meliefste K, Lewne M, Gehring U, Bellander T, Fischer P, van Vliet P, Brauer M, Wichmann HE, and Brunekreef B. 2003a. Comparison between different traffic-related particle indicators: Elemental carbon (EC), PM_{2.5} mass, and absorbance. *J Expo Analysis Environ Epidemiol* 13:134–43.
- Cyrys J, Stölzel M, Heinrich J, Kreyling WG, Menzel N, Wittmaack K, Tuch T, and Wichmann H. 2003b. Elemental composition and sources of fine and ultrafine ambient particles in Erfurt, Germany. *Sci Total Env* 305:143–56.
- Dagher Z, Garçon G, Gosset P, Ledoux F, Surpateanu G, Courcot D, Aboukais A, Puskaric E, and Shirali P. 2005. Pro-inflammatory effects of Dunkerque city air pollution particulate matter 2.5 in human epithelial lung cells (L132) in culture. *J Appl Toxicol* 25:166–75.
- Dagher Z, Garçon G, Billet S, Gosset P, Ledoux F, Courcot D, Aboukais A, and Shirali P. 2006. Activation of different pathways of apoptosis by air pollution particulate matter (PM_{2.5}) in human epithelial lung cells (L132) in culture. *Toxicology* 225:12–24.
- Dai J, Xie C, and Churg A. 2002. Iron loading makes a nonfibrogenic model air pollutant particle fibrogenic in rat tracheal explants. *Am J Respir Cell Mol Biol* 26:685–93.
- Dai J, Xie C, Vincent R, and Churg A. 2003. Air pollution particles produce airway wall remodeling in rat tracheal explants. *Am J Respir Cell Mol Biol* 29:352–8.
- Daigle CC, Chalupa DC, Gibb FR, Morrow PE, Oberdörster G, Utell MJ, and Frampton MW. 2003. Ultrafine particle deposition in humans during rest and exercise. *Inhal Toxicol* 15:539–52.
- Dales R, Burnett RT, Smith-Doiron M, Stieb DM, and Brook JR. 2004. Air pollution and sudden infant death syndrome. *Pediatrics* 113:e628–31.
- Daniels MJ, Dominici F, Samet JM and Zeger SL. 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 MJ; Dominici F; Zeger SL; Samet JM. 2004. The national morbidity, mortality, and air pollution study Part III: PM₁₀ concentration-response curves and thresholds for the 20 largest US cities. Health Effects Institute Report 94, Part III. Boston, MA.
- Davidson JH and McKinney PJ. 1998. Chemical vapor deposition in the corona discharge of electrostatic air cleaners. *Aerosol Sci Tech* 29:102–10.
- de Haar C, Hassing I, Bol M, Bleumink R, and Pieters R. 2005. Ultrafine carbon black particles cause early airway inflammation and have adjuvant activity in a mouse allergic airway disease model. *Toxicol Sci* 87:409–18.

- de Haar C, Hassing I, Bol M, Bleumink R, and Pieters R. 2006. Ultrafine but not fine particulate matter causes airway inflammation and allergic airway sensitization to co-administered antigen in mice. *Clin Exp Allergy* 36:1469–79.
- de Hartog JJ, Hoek G, Peters A, Timonen KL, Ibaldo-Mulli A, Brunekreef B, Heinrich J, Tiittanen P, van Wijnen JH, Kreyling W, Kulmala M, and Pekkanen J. 2003. Effects of fine and ultrafine particles on cardiorespiratory symptoms in elderly subjects with coronary heart disease: the ULTRA study. *Am J Epidemiol* 157:613–23.
- de Kok TM, Hogervorst JG, Briede JJ, van Herwijnen MH, Maas LM, Moonen EJ, Drieste HA, and Kleinjans JC. 2005. Genotoxicity and physicochemical characteristics of traffic-related ambient particulate matter. *Environ Mol Mutagen* 46:71–80.
- De Leon SF, Thurston GD, and Ito K. 2003. Contribution of respiratory disease to nonrespiratory mortality associations with air pollution. *Am J Respir Crit Care Med* 167:1117–23.
- De Paula Santos U, Terra Filho M, Ferreira Braga AL, Amador Pereira LA, Lin CA, Hilário Do Nascimento Saldiva P, Artigas Giorgi DM, Grupi CJ, Bussacos MA, and Trevisan Zanetta DM. 2005. Effects of air pollution on blood pressure and heart rate variability: A panel study of vehicular traffic controllers in the city of Sao Paulo, Brazil. *Eur Heart J* 26:193–200.
- De Vizcaya Ruiz A, Gutierrez Castillo ME, Uribe Ramirez M, Cebrian ME, Mugica Alvarez V, Sepulveda J, Rosas I, Salinas E, Garcia Cuellar C, Martinez F, Alfaro Moreno E, Torres Flores V, Osornio Vargas A, Sioutas C, Fine PM, Singh M, Geller MD, Kuhn T, Miguel AH, Eiguren Fernandez A, Schiestl RH, Reliene R, and Froines J. 2006. Characterization and *in vitro* biological effects of concentrated particulate matter from Mexico City. *Atmos Environ* 40 Suppl. 2:S583–92.
- Delfino RJ, Zeiger RS, Seltzer JM, Street DH, and McLaren CE. 2002. Association of asthma symptoms with peak particulate air pollution and effect modification by anti-inflammatory medication use. *Environ Health Perspect* 110:A607–17.
- Delfino RJ, Gong H Jr, Linn WS, Pellizzari ED, and Hu Y. 2003. Asthma symptoms in Hispanic children and daily ambient exposures to toxic and criteria air pollutants. *Environ Health Perspect* 111:647–56.
- Delfino RJ, Quintana PJ, Floro J, Gastanaga VM, Samimi BS, Kleinman MT, Liu LJ, Bufalino C, Wu CF, and McLaren CE. 2004. Association of FEV₁ in asthmatic children with personal and microenvironmental exposure to airborne particulate matter. *Environ Health Perspect* 112:932–41.
- Delfino RJ, Staimer N, Gillen D, Tjoa T, Sioutas C, Fung K, George SC, and Kleinman MT. 2006. Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma. *Environ Health Perspect* 114:1736–43.
- DeMeo DL, Zanobetti A, Litonjua AA, Coull BA, Schwartz J, and Gold DR. 2004. Ambient air pollution and oxygen saturation. *Am J Respir Crit Care Med* 170:383–7.
- Desqueyroux H, Pujet JC, Prosper M, Le Moullec Y, and Momas I. 2002. Effects of air pollution on adults with chronic obstructive pulmonary disease. *Arch Environ Health* 57:554–60.
- Devlin RB, Ghio AJ, Kehrl H, Sanders G, and Cascio W. 2003. Elderly humans exposed to concentrated air pollution particles have decreased heart rate variability. *Eur Respir J Suppl* 40:76s–80s.
- Dewanji A and Moolgavkar SH. 2000. A Poisson process approach for recurrent event data with environmental covariates. *Environmetrics* 11:665–73.

- Diaz J, Linares C, Garcia-Herrera R, Lopez C, and Trigo R. 2004. Impact of temperature and air pollution on the mortality of children in Madrid. *J Occup Environ Med* 46:768–74.
- Dick CA, Brown DM, Donaldson K, and Stone V. 2003a. The role of free radicals in the toxic and inflammatory effects of four different ultrafine particle types. *Inhal Toxicol* 15:39–52.
- Dick CA, Singh P, Daniels M, Evansky P, Becker S, and Gilmour MI. 2003b. Murine pulmonary inflammatory responses following instillation of size-fractionated ambient particulate matter. *J Toxicol Environ Health A* 66:2193–2207.
- Diez-Roux AV, Auchincloss AH, Astor B, Barr RG, Cushman M, Dvorchak T, Jacobs DR Jr, Kaufman J, Lin X, and Samson P. 2006. Recent exposure to particulate matter and C-reactive protein concentration in the multi-ethnic study of atherosclerosis. *Am J Epidemiol* 164:437–48.
- D'Ippoliti D, Forastiere F, Ancona C, Agabiti N, Fusco D, Michelozzi P, and Perucci CA. 2003. Air pollution and myocardial infarction in Rome: a case-crossover analysis. *Epidemiology* 14:528–35.
- Dockery DW and Spengler JD. 1981. Indoor–outdoor relationships of respirable sulfates and particles. *Atmos Env* 15:335–43.
- Dockery DW, Speizer FE, Stram DO, Ware JH, Spengler JD, and Ferris BG. 1989. Effects of inhalable particles on respiratory health of children. *Am Rev Respir Dis* 139:587–94.
- Dockery DW, Pope CA, Xu X, Spengler JD, Ware JH, Fay ME, Ferris BG Jr, and Speizer FE. 1993. An association between air pollution and mortality in six U.S. cities. *N Engl J Med* 329:1753–9.
- Dockery DW, Luttmann-Gibson H, Rich DQ, Link MS, Mittleman MA, Gold DR, Koutrakis P, Schwartz JD, and Verrier RL. 2005. Association of air pollution with increased incidence of ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. *Environ Health Perspect* 113:670–4.
- Dominici F, Zeger SL, and Samet JM. 2000. A measurement error model for time-series studies of air pollution and mortality. *Biostatistics* 1:157–75.
- Dominici F, McDermott A, Zeger SL, and Samet JM. 2003a. National maps of the effects of particulate matter on mortality: exploring geographical variation. *Environ Health Perspect* 111:39–44.
- Dominici F, McDermott A, Zeger SL, and Samet JM. 2003b. Airborne particulate matter and mortality: timescales effects in four cities. *Am J Epidemiol* 157:1055–65.
- Dominici F, Zanobetti A, Zeger SL, Schwartz J, and Samet JM. 2004. Hierarchical bivariate time series models: a combined analysis of the effects of particulate matter on morbidity and mortality. *Biostatistics* 5:341–60.
- Dominici F, McDermott A, Daniels M, Zeger SL, and Samet JM. 2005. Revised analyses of the National Morbidity, Mortality, and Air Pollution Study: mortality among residents of 90 cities. *J Tox Environ Health A* 68:1071–92.
- Dominici F, Peng RD, Bell ML, Pham L, McDermott A, Zeger SL, and Samet JM. 2006. Fine particulate air pollution and hospital admission for cardiovascular and respiratory diseases. *JAMA* 295:1127–34.
- Dorman DC, Brenneman KA, McElveen AM, Lynch SE, Roberts KC, and Wong BA. 2002. Olfactory transport: a direct route of delivery of inhaled manganese phosphate to the rat brain. *J Toxicol Environ Health A* 65:1493–511.

- Dubowsky SD, Suh H, Schwartz J, Coull BA, and Gold DR. 2006. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. *Environ Health Perspect* 114:992–8.
- Dugandzic R, Dodds L, Stieb D, and Smith-Doiron M. 2006. The association between low level exposures to ambient air pollution and term low birth weight: a retrospective cohort study. *Environ Health* 5:3.
- Dvonch JT, Brook RD, Keeler GJ, Rajagopalan S, D'Alecy LG, Marsik FJ, Morishita M, Yip FY, Brook JR, Timm EJ, Wagner JG, and Harkema JR. 2004. Effects of concentrated fine ambient particles on rat plasma levels of asymmetric dimethylarginine. *Inhal Toxicol* 16:473–80.
- Ebelt ST, Petkau AJ, Vedal S, Fisher TV, and Brauer M. 2000. Exposure of chronic obstructive pulmonary disease patients to particulate matter: relationships between personal and ambient air concentrations. *J Air Waste Man Assoc* 50:1081–94.
- Ebelt ST, Wilson WE, and Brauer M. 2005. Exposure to ambient and nonambient components of particulate matter: a comparison of health effects. *Epidemiology* 16:396–405.
- Eilstein D, Declercq C, Prouvost H, Pascal L, Nunes C, Filleul L, Cassadou S, Le Tertre A, Zeghnoun A, Medina S, Lefranc A, Saviuc P, and Quenel PCD. 2004. [The impact of air pollution on health. The "Programme de surveillance air et santé" (Air and Health Surveillance Program)]. *Presse Med* 33:1323–7.
- Elder A and Oberdorster G. 2006. Translocation and effects of ultrafine particles outside of the lung. *Clin Occup Environ Med* 5:785–96.
- Elder AC, Gelein R, Azadniv M, Frampton M, Finkelstein J, and Oberdörster G. 2004a. Systemic effects of inhaled ultrafine particles in two compromised, aged rat strains. *Inhal Toxicol* 16:461–71.
- Elder A, Gelein R, Finkelstein J, Phipps R, Frampton M, Utell M, Kittelson DB, Watts WF, Hopke P, Jeong CH, Kim E, Liu W, Zhao W, Zhuo L, Vincent R, Kumarathasan P, and Oberdörster G. 2004b. On-road exposure to highway aerosols. 2. Exposures of aged, compromised rats. *Inhal Toxicol* 16 Suppl 1:41–53.
- Elder A, Gelein R, Finkelstein JN, Driscoll KE, Harkema J, and Oberdörster G. 2005. Effects of subchronically inhaled carbon black in three species. I. Retention kinetics, lung inflammation, and histopathology. *Toxicol Sci* 88:614–29.
- Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, Potter R, Maynard A, Ito Y, Finkelstein J, and Oberdörster G. 2006. Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. *Environ Health Perspect* 114:1172–8.
- Emmerich SJ and Nabinger SJ. 2001. Measurement and simulation of the IAQ impact of particle air cleaners in a single-zone building. *HVAC & R Research* 7:223–44.
- Environment Canada. 2006. National Air Pollution Surveillance (NAPS) Network – Annual data summary for 2004. Report 7/AP/38 Revised, Environmental Science and Technology Centre. ISBN 978-0-662-69727-5. Available at www.etc-ect.ec.gc.ca/publications/napsreports_e.html
- Environment Canada. 2011. Canadian Smog Science Assessment. Final Supporting Document. Volume 1. Atmospheric Science and Environmental Effects. Available upon request from enviroinfo@ec.gc.ca.
- Environment Canada and Health Canada. 2011. Canadian Smog Science Assessment: Highlights and Key Messages. ISBN 978-1-100-19063-1. Cat. No.: En88-5/2011E.

- Enstrom JE. 2005. Fine particulate air pollution and total mortality among elderly Californians, 1973–2002. *Inhal Toxicol* 17:803–16.
- Erbas B and Hyndman RJ. 2005. Sensitivity of the estimated air pollution-respiratory admissions relationship to statistical model choice. *Int J Environ Health Res* 15:437–48.
- Erbas B, Kelly AM, Physick B, Code C, and Edwards M. 2005. Air pollution and childhood asthma emergency hospital admissions: estimating intra-city regional variations. *Int J Environ Health Res* 15:11–20.
- Erdinger L, Durr M, and Hopker KA. 2005. Correlations between mutagenic activity of organic extracts of airborne particulate matter, NO_x and sulphur dioxide in southern Germany: results of a two-year study. *Environ Sci Pollut Res Int* 12:10–20.
- Evans GF, Highsmith RV, Sheldon LS, Suggs JC, Williams RW, Zweidinger RB, Creason JP, Walsh D, Rodes CE, and Lawless PA. 2000. The 1999 Fresno particulate matter exposure studies: comparison of community, outdoor and residential PM mass measurements. *J Air Waste Man Assoc* 50:1887–96.
- Farhat SC, Paulo RL, Shimoda TM, Conceicao GM, Lin CA, Braga AL, Warth MP, and Saldiva PH. 2005. Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. *Braz J Med Biol Res* 38:227–35.
- Fellin P and Otson R. Emissions of VPOC from residences in the metropolitan Toronto area. A&WMA 1997. *In Proceedings of the 90th annual meeting and exhibition of the Air and Waste Management Association, Toronto (ON), 8–13 Jun 1997. CONF-970677.*
- Fernvik E, Peltre G, Senechal H, and Vargaftig BB. 2002. Effects of birch pollen and traffic particulate matter on Th2 cytokines, immunoglobulin E levels and bronchial hyper-responsiveness in mice. *Clin Exp Allergy* 32:602–11.
- Filleul L, Baldi I, Dartigues JF, and Tessier JF. 2003. Risk factors among elderly for short term deaths related to high levels of air pollution. *Occup Environ Med* 60:684–8.
- Filleul L, Le Tertre A, Baldi I, and Tessier JF. 2004a. Difference in the relation between daily mortality and air pollution among elderly and all-ages populations in southwestern France. *Environ Res* 94:249–53.
- Filleul L, Rondeau V, Cantagrel A, Dartigues JF, and Tessier JF. 2004b. Do subject characteristics modify the effects of particulate air pollution on daily mortality among the elderly? *J Occup Environ Med* 46:1115–22.
- Filleul L, Rondeau V, Vandentorren S, Le Moual N, Cantagrel A, and Annesi-Maesano I. 2005. Twenty five year mortality and air pollution: results from the French PAARC survey. *Occup Environ Med* 62:453–60.
- Filleul L, Zeghnoun A, Cassadou S, Declercq C, Eilstein D, le Tertre A, Medina S, Pascal L, Prouvost H, Saviuc P, and Quenel P. 2006. Influence of set-up conditions of exposure indicators on the estimate of short-term associations between urban pollution and mortality. *Sci Total Environ* 355:90–7.
- Finkelstein MM, Jerrett M, DeLuca P, Finkelstein N, Verma DK, and Chapman K. 2003. Relation between income, air pollution and mortality: a cohort study. *CMAJ* 169:397–402.
- Fischer PH, Steerenberg PA, Snelder JD, van Loveren H, and van Amsterdam JG. 2002. Association between exhaled nitric oxide, ambient air pollution and respiratory health in school children. *Int Arch Occup Environ Health* 75:348–53.

- Fischer P, Hoek G, Brunekreef B, Verhoeff A, and van Wijnen J. 2003. Air pollution and mortality in the Netherlands: are the elderly more at risk? *Eur Respir J Suppl* 40:34s–38s.
- Fisk WJ, Faulkner D, Sullivan D, and Mendell MJ. 2000. Particle concentrations and sizes with normal and high efficiency air filtration in a sealed air-conditioned office building. *Aerosol Sci Tech* 32:527–44.
- Fisk WJ, Faulkner D, Palonen J, and Seppanen O. 2002. Performance and costs of particle air filtration technologies. *Indoor Air* 12:223–34.
- Fixler DE. 2005. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997–2000. *Am J Epidemiol* 162:238–52.
- Forastiere F, Stafoggia M, Picciotto S, Bellander T, D'Ippoliti D, Lanki T, von Klot S, Nyberg F, Paatero P, Peters A, Pekkanen J, Sunyer J, and Perucci CA. 2005. A case-crossover analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. *Am J Respir Crit Care Med* 172:1549–55.
- Forastiere F, Stafoggia M, Tasco C, Picciotto S, Agabiti N, Cesaroni G, and Perucci CA. 2007. Socioeconomic status, particulate air pollution, and daily mortality: Differential exposure or differential susceptibility. *Am J Ind Med* 50:208–216 (pre-published online in 2006).
- Frampton MW, Utell MJ, Zareba W, Oberdörster G, Cox C, Huang LS, Morrow PE, Lee FE, Chalupa D, Frasier LM, Speers DM, and Stewart J. 2004. Effects of exposure to ultrafine carbon particles in healthy subjects and subjects with asthma. *Res Rep Health Eff Inst* 126:1–47; disc. 49–63.
- Frampton MW, Stewart JC, Oberdörster G, Morrow PE, Chalupa D, Pietropaoli AP, Frasier LM, Speers DM, Cox C, Huang LS, and Utell MJ. 2006. Inhalation of ultrafine particles alters blood leukocyte expression of adhesion molecules in humans. *Environ Health Perspect* 114: 51–8.
- Franck U, Herbarth O, Wehner B, Wiedensohler A, and Manjarrez M. 2003. How do the indoor size distributions of airborne submicron and ultrafine particles in the absence of significant indoor sources depend on outdoor distributions? *Indoor Air* 13:174–81.
- Franklin M, Zeka A, and Schwartz J. 2007. Association between $PM_{(2.5)}$ and all-cause and specific-cause mortality in 27 US communities. *J Expo Sci Environ Epidemiol* 17:279–287 (pre-published online in 2006).
- Fromme H, Lahrz T, Piloty A, Gebhardt H, Oddoy A, and Ruden H. 2004. Polycyclic aromatic hydrocarbons inside and outside of apartments in an urban area. *Sci Total Env* 326:143–9.
- Frye C, Hoelscher B, Cyrus J, Wjst M, Wichmann HE, and Heinrich J. 2003. Association of lung function with declining ambient air pollution. *Environ Health Perspect* 111:383–7.
- Fuentes M, Song HR, Ghosh SK, Holland DM, and Davis JM. 2006. Spatial association between speciated fine particles and mortality. *Biometrics* 62: 855–63.
- Fujii T, Hayashi S, Hogg JC, Mukae H, Suwa T, Goto Y, Vincent R, and van Eeden SF. 2002. Interaction of alveolar macrophages and airway epithelial cells following exposure to particulate matter produces mediators that stimulate the bone marrow. *Am J Respir Cell Mol Biol* 27:34–41.
- Fujii T, Hogg JC, Keicho N, Vincent R, Van Eeden SF, and Hayashi S. 2003. Adenoviral E1A modulates inflammatory mediator expression by lung epithelial cells exposed to PM_{10} . *Am J Physiol Lung Cell Mol Physiol* 284:L290–7.
- Fung K, Chow JC, and Watson JG. 2002. Evaluation of OC/EC speciation by thermal manganese dioxide oxidation and the improve method. *J Air & Waste Manage Assoc* 52:1333–41.

- Fung KY, Luginaah I, Gorey KM, and Webster G. 2005a. Air pollution and daily hospital admissions for cardiovascular diseases in Windsor, Ontario. *Can J Public Health* 96:29–33.
- Fung KY, Gorey KM, Luginaah I, and Webster G. 2005b. Air pollution and daily hospitalization rates for cardiovascular and respiratory diseases in London, Ontario. *Int J Environ Stud* 62:677–85.
- Fung KY, Khan S, Krewski D, Chen Y, Fung KY, Khan S, Krewski D, and Chen Y. 2006. Association between air pollution and multiple respiratory hospitalizations among the elderly in Vancouver, Canada. *Inhal Tox* 18:1005–11.
- Furuyama A, Hirano S, Koike E, and Kobayashi T. 2006. Induction of oxidative stress and inhibition of plasminogen activator inhibitor-1 production in endothelial cells following exposure to organic extracts of diesel exhaust particles and urban fine particles. *Arch Toxicol* 80:154–62.
- Galan I, Tobias A, Banegas JR, and Aranguéz E. 2003. Short-term effects of air pollution on daily asthma emergency room admissions. *Eur Respir J* 22:802–8.
- Gao F, Barchowsky A, Nemeč AA, and Fabisiak JP. 2004. Microbial stimulation by *Mycoplasma fermentans* synergistically amplifies IL-6 release by human lung fibroblasts in response to residual oil fly ash (ROFA) and nickel. *Toxicol Sci* 81:467–79.
- Garçon G, Dagher Z, Zerimech F, Ledoux F, Courcot D, Aboukais A, Puskaric E, and Shirali P. 2006. Dunkerque City air pollution particulate matter-induced cytotoxicity, oxidative stress and inflammation in human epithelial lung cells (L132) in culture. *Toxicol in Vitro* 20:519–28.
- Gardner SY, McGee JK, Kodavanti UP, Ledbetter A, Everitt JI, Winsett DW, Doerfler DL, and Costa DL. 2004. Emission-particle-induced ventilatory abnormalities in a rat model of pulmonary hypertension. *Environ Health Perspect* 112:872–8.
- Gauderman WJ, Avol E, Gilliland F, Vora H, Thomas D, and Berhane K. 2004. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med* 351:1057–67.
- Gavett SH, Haykal-Coates N, Copeland LB, Heinrich J, and Gilmour MI. 2003. Metal composition of ambient PM_{2.5} influences severity of allergic airways disease in mice. *Environ Health Perspect* 111:1471–7.
- Gehring U, Heinrich J, Kramer U, Grote V, Hochadel M, and Sugiri D. 2006. Long-term exposure to ambient air pollution and cardiopulmonary mortality in women. *Epidemiology* 17:545–51.
- Geiser M, Rothen-Rutishauser B, Kapp N, Schurch S, Kreyling W, Schulz H, Semmler M, Im Hof V, Heyder J, and Gehr P. 2005. Ultrafine particles cross cellular membranes by nonphagocytic mechanisms in lungs and in cultured cells. *Environ Health Perspect* 113:1555–60.
- Geller MD, Chang MH, Sioutas C, Ostro BD, and Lipsett MJ. 2002. Indoor/outdoor relationship and chemical composition of fine and coarse particles in the Southern California deserts. *Atmos Env* 36:1099–1110.
- Geller MD, Ntziachristos L, Mamakos A, Samaras Z, Schmitz DA, Froines JR, and Sioutas C. 2006. Physicochemical and redox characteristics of particulate matter (PM) emitted from gasoline and diesel passenger cars. *Atmos Environ* 40: 6988–7004.
- Gent JF, Triche EW, Holford TR, Belanger K, Bracken MB, Beckett WS, and Leaderer BP. 2003. Association of low-level ozone and fine particles with respiratory symptoms in children with asthma. *JAMA* 290:1859–67.

- Georgiadis P, Stoikidou M, Topinka J, Kaila S, Gioka M, Katsouyanni K, Sram R, and Kyrtopoulos SA. 2001. Personal exposures to PM_{2.5} and polycyclic aromatic hydrocarbons and their relationship to environmental tobacco smoke at two locations in Greece. *J Expo Analysis Environ Epidemiol* 11:169–83.
- Gerlofs-Nijland ME, Boere AJ, Leseman DL, Dormans JA, Sandstrom T, Salonen RO, van Bree L, and Cassee FR. 2005. Effects of particulate matter on the pulmonary and vascular system: time course in spontaneously hypertensive rats. *Part Fibre Toxicol* 2:2.
- Ghio AJ, Kim C, and Devlin RB. 2000. Concentrated ambient air particles induce mild pulmonary inflammation in healthy human volunteers. *Am J Respir Crit Care Med* 162:981–8.
- Ghio AJ, Hall A, Bassett MA, Cascio WE, and Devlin RB. 2003. Exposure to concentrated ambient air particles alters hematologic indices in humans. *Inhal Toxicol* 15:1465–78.
- Gilboa SM, Mendola P, Olshan AF, Langlois PH, Savitz DA, Loomis D, Herring AH, and Fixler DE. 2005. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997–2000. *Am J Epidemiol* 162:238–52.
- Gilliland FD, Berhane K, Rappaport EB, Thomas DC, Avol E, Gauderman WJ, London SJ, Margolis HG, McConnell R, Islam KT, and Peters JM. 2001. The effects of ambient air pollution on school absenteeism due to respiratory illnesses. *Epidemiology* 12:43–54.
- Gilmour MI, O'Connor S, Dick CA, Miller CA, and Linak WP. 2004a. Differential pulmonary inflammation and *in vitro* cytotoxicity of size-fractionated fly ash particles from pulverized coal combustion. *J Air Waste Manag Assoc* 54:286–95.
- Gilmour PS, Schladweiler MC, Richards JH, Ledbetter AD, and Kodavanti UP. 2004b. Hypertensive rats are susceptible to TLR4-mediated signaling following exposure to combustion source particulate matter. *Inhal Toxicol* 16 Suppl 1:5–18.
- Gilmour PS, Ziesenis A, Morrison ER, Vickers MA, Drost EM, Ford I, Karg E, Mossa C, Schroepfel A, Ferron GA, Heyder J, Greaves M, MacNee W, and Donaldson K. 2004c. Pulmonary and systemic effects of short-term inhalation exposure to ultrafine carbon black particles. *Toxicol Appl Pharmacol* 195:35–44.
- Gilmour PS, Morrison ER, Vickers MA, Ford I, Ludlam CA, Greaves M, Donaldson K, and MacNee W. 2005. The procoagulant potential of environmental particles (PM₁₀). *Occup Environ Med* 62:164–71.
- Girardot SP, Ryan PB, Smith SM, Davis WT, Hamilton CB, Obenour RA, Renfro JR, Tromatore KA, and Reed GD. 2006. Ozone and PM_{2.5} exposure and acute pulmonary health effects: a study of hikers in the Great Smoky Mountains National Park. *Environ Health Perspect* 114:1044–52.
- Godleski JJ, Clarke RW, Coull BA, Saldiva PHN, Jiang N-F, Lawrence J, and Koutrakis, P. 2002. Composition of inhaled urban air particles determines acute pulmonary responses. *Ann Occup Hyg* 46 Suppl 1:419–24.
- Gold DR, Litonjua AA, Zanobetti A, Coull BA, Schwartz J, MacCallum G, Verrier RL, Nearing BD, Canner MJ, Suh H, and Stone PH. 2005. Air pollution and ST-segment depression in elderly subjects. *Environ Health Perspect* 113:883–7.
- Goldberg MS, Bailar JCI, Burnett RT, Brook JR, Tamblyn R, Bonvalot Y, Ernst P, Flegel KM, Singh R, and 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 No. 97:7–113.

- Goldberg MS, Burnett RT, Yale JF, Valois MF, and Brook JR. 2006. Associations between ambient air pollution and daily mortality among persons with diabetes and cardiovascular disease. *Environ Res* 100:255–267.
- Goldsmith CA, Ning Y, Qin G, Imrich A, Lawrence J, Murthy GG, Catalano PJ, and Kobzik L. 2002. Combined air pollution particle and ozone exposure increases airway responsiveness in mice. *Inhal Toxicol* 14:325–47.
- Gong H, Linn WS, Terrell SL, Anderson KR, Clark KW, Sioutas C, Cascio WE, Alexis N, and Devlin RB. 2004. Exposures of elderly volunteers with and without chronic obstructive pulmonary disease (COPD) to concentrated ambient fine particulate pollution. *Inhal Toxicol* 16:731–44.
- Gong H, Linn W, Clark K, Anderson K, Geller M, and Sioutas C. 2005. Respiratory responses to exposures with fine particulates and nitrogen dioxide in the elderly with and without COPD. *Inhal Toxicol* 17:123–32.
- Gordian ME and Choudhury AH. 2003. PM₁₀ and asthma medication in schoolchildren. *Arch Environ Health* 58:42–7.
- Goss CH, Newsom SA, Schildcrout JS, Sheppard L, and Kaufman JD. 2004. Effect of ambient air pollution on pulmonary exacerbations and lung function in cystic fibrosis. *Am J Respir Crit Care Med* 169:816–21.
- Goswami E, Larson T, Lumley T, and Liu LJS. 2002. Spatial characteristics of fine particulate matter: identifying representative monitoring locations in Seattle, Washington. *J Air Waste Man Assoc* 52:324–33.
- Goto Y, Hogg JC, Shih CH, Ishii H, Vincent R, and van Eeden SF. 2004a. Exposure to ambient particles accelerates monocyte release from bone marrow in atherosclerotic rabbits. *Am J Physiol Lung Cell Mol Physiol* 287:L79–85.
- Goto Y, Ishii H, Hogg JC, Shih CH, Yatera K, Vincent R, and van Eeden SF. 2004b. Particulate matter air pollution stimulates monocyte release from the bone marrow. *Am J Respir Crit Care Med* 170:891–7.
- Götschi T, Oglesby L, Mathys P, Monn C, Manalis N, Koistinen K, Jantunen M, Hänninen O, Polanska L, and Kunzli N. 2002. Comparison of black smoke and PM_{2.5} levels in indoor and outdoor environments of four European cities. *Environ Sci Technol* 36:1191–97.
- Gouveia N, Bremner SA, and Novaes HM. 2004. Association between ambient air pollution and birth weight in Sao Paulo, Brazil. *J Epidemiol Community Health* 58:11–7.
- Gower SK and McColl S. 2005. Development of the PEARLS model (Particulate Exposure from Ambient to Regional Lung by Subgroup) and use of Monte Carlo Simulation to predict internal exposure to PM in Toronto. *Risk Anal* 25:301–15.
- Graff DW, Cascio WE, Brackhan JA, and Devlin RB. 2004. Metal particulate matter components affect gene expression and beat frequency of neonatal rat ventricular myocytes. *Environ Health Perspect* 112:792–8.
- Grahame TJ and Schlesinger RB. 2007. Health effects of airborne particulate matter: do we know enough to consider regulating specific particle types or sources? *Inhal Tox* 19:457–81.
- Greenwell LL, Moreno T, and Richards RJ. 2003. Pulmonary antioxidants exert differential protective effects against urban and industrial particulate matter. *J Biosci* 28:101–7.
- Grgic B, Finlay WH, Burnell PKP, and Heenan AF. 2004. *In vitro* intersubject and intrasubject deposition measurements in realistic mouth-throat geometries. *J Aerosol Sci* 35:1025–40.

- Grippi MA. 1995. *Pulmonary Pathophysiology*. Philadelphia PA: Lippincott, Williams and Wilkins.
- Gurgueira SA, Lawrence J, Coull B, Murthy GG, and Gonzalez-Flecha B. 2002. Rapid increases in the steady-state concentration of reactive oxygen species in the lungs and heart after particulate air pollution inhalation. *Environ Health Perspect* 110:749–55.
- Gursinsky T, Ruhs S, Friess U, Diabate? S, Krug HF, Silber R-E, and Simm A. 2006. Air pollution-associated fly ash particles induce fibrotic mechanisms in primary fibroblasts. *Biol Chem* 387:1411–20.
- Gutierrez-Castillo ME, Roubicek DA, Cebrian-Garcia ME, De Vizcaya-Ruiz A, Sordo-Cedeno M, and Ostrosky-Wegman P. 2006. Effect of chemical composition on the induction of DNA damage by urban airborne particulate matter. *Environ Mol Mutagen* 47:199–211.
- Ha EH, Lee JT, Kim H, Hong YC, Lee BE, Park HS, and Christiani DC. 2003. Infant susceptibility of mortality to air pollution in Seoul, South Korea. *Pediatrics* 111:284–90.
- Hajat S, Haines A, Atkinson RW, Bremner SA, Anderson HR, and Emberlin J. 2001. Association between air pollution and daily consultations with general practitioners for allergic rhinitis in London, United Kingdom. *Am J Epidemiol* 153:704–14.
- Hamada K, Goldsmith CA, Suzuki Y, Goldman A, and Kobzik L. 2002. Airway hyperresponsiveness caused by aerosol exposure to residual oil fly ash leachate in mice. *J Toxicol Environ Health A* 65:1351–65.
- Hämeri K, Hussein T, Kulmala M, and Aalto P. 2004. Measurements of fine and ultrafine particles in Helsinki: connection between outdoor and indoor air quality. *Boreal Environ Res* 9:459–67.
- Hamilton RF Jr, Holian A, and Morandi MT. 2004. A comparison of asbestos and urban particulate matter in the *in vitro* modification of human alveolar macrophage antigen-presenting cell function. *Exp Lung Res* 30:147–62.
- Hanley JT, Ensor DS, Smith DD, and Sparks LE. 1994. Fractional aerosol filtration efficiency of in-duct ventilation air cleaners. *Indoor Air* 4:169–78.
- Hanley JT and Elion JM. 2005. Coordinate and Analyze Interlaboratory Testing of Filters under ASHRAE Standard 52.2 to Determine the Adequacy of the Apparatus Qualification Tests. Atlanta, GA: ASHRAE Project No. 1088-RP. RTI project No 08200. Final report.
- Hänninen OO, Lebet E, Ilacqua V, Katsouyanni K, Kunzli F, Sram RJ, and Jantunen M. 2004. Infiltration of ambient PM_{2.5} and levels of indoor generated non-ETS PM_{2.5} in residences of four European cities. *Atmos Env* 38:6411–423.
- Hänninen OO, Tuomisto JT, Jantunen MJ, and Lebet E. 2005a. Characterization of model error in a simulation of fine particulate matter exposure distributions of the working age population in Helsinki, Finland. *J Air Waste Man Assoc* 55:446–57.
- Hänninen OO, Palonen J, Tuomisto JT, Yli-Tuomi T, Seppanen O, and Jantunen MJ. 2005b. Reduction potential of urban PM_{2.5} mortality risk using modern ventilation systems in buildings. *Indoor Air* 15:246–56.
- Hansen C, Neller A, Williams G, and Simpson R. 2006. Maternal exposure to low levels of ambient air pollution and preterm birth in Brisbane, Australia. 2006. *BJOG* 113:935–41.
- Hapcioglu B, Issever H, Kocyigit E, Disci R, Vatansever S, and Ozdilli K. 2006. The effect of air pollution and meteorological parameters on chronic obstructive pulmonary disease at an Istanbul hospital. *Indoor Built Env* 15:147–53.

- Harder V, Gilmour P, Lentner B, Karg E, Takenaka S, Ziesenis A, Stampfl A, Kodavanti U, Heyder J, and Schulz H. 2005. Cardiovascular responses in unrestrained WKY rats to inhaled ultrafine carbon particles. *Inhal Toxicol* 17:29–42.
- Harkema JR, Keeler G, Wagner J, Morishita M, Timm E, Hotchkiss J, Marsik F, Dvonch T, Kaminski N, and Barr E. 2004. Effects of concentrated ambient particles on normal and hypersecretory airways in rats. *Res Rep Health Eff Inst* 120:1–79.
- Harrabi I, Rondeau V, Dartigues JF, Tessier JF, and Filleul L. 2006. Effects of particulate air pollution on systolic blood pressure: a population-based approach. *Environ Res* 101:89–93.
- He C, Morawska L, and Gilbert D. 2005. Particle deposition rates in residential houses. *Atmos Env* 39:3891–99.
- Healey K, Lingard JJ, Tomlin AS, Hughes A, White KL, Wild CP, and Routledge MN. 2005. Genotoxicity of size-fractionated samples of urban particulate matter. *Environ Mol Mutagen* 45:380–7.
- Healey K, Smith EC, Wild CP, and Routledge MN. 2006. The mutagenicity of urban particulate matter in an enzyme free system is associated with the generation of reactive oxygen species. *Mutat Res* 602:1–6.
- Health Canada and Environment Canada. 1999. National Ambient Air Quality Objectives for Particulate Matter Part 1: Science Assessment Document. Ottawa, ON:10-1 to 10-28.
- Hedley AJ, Wong CM, Thach TQ, Ma S, Lam TH, and Anderson HR. 2002. Cardiorespiratory and all-cause mortality after restrictions on sulphur content of fuel in Hong Kong: an intervention study. *The Lancet* 360: 1646-52.
- HEI (Health Effects Institute). 2003. Revised analyses of time-series studies of air pollution and health. Special Report, Health Effects Institute. Boston, MA.
- Heinrich J, Hoelscher B, Frye C, Meyer I, Pitz M, Cyrus J, Wjst M, Neas L, and Wichmann HE. 2002. Improved air quality in reunified Germany and decreases in respiratory symptoms. *Epidemiology* 13:394–401.
- Henneberger A, Zareba W, Ibalid-Mulli A, Ruckerl R, Cyrus J, Couderc JP, Mykins B, Woelke G, Wichmann HE, and Peters A. 2005. Repolarization changes induced by air pollution in ischemic heart disease patients. *Environ Health Perspect* 113:440–6.
- Heraty K and Quinlan N. Computational modelling of flow in ideal and realistic airway bifurcations. American Society of Mechanical Engineers. 2004. *In Proceedings, International Mechanical Engineering Congress and Exposition (November 13–20, 2004), Anaheim, CA.*
- Hetland RB, Cassee FR, Refsnes M, Schwarze PE, Lag M, Boere AJ, and Dybing E. 2004. Release of inflammatory cytokines, cell toxicity and apoptosis in epithelial lung cells after exposure to ambient air particles of different size fractions. *Toxicol in Vitro* 18:203–12.
- Hetland RB, Cassee FR, Lag M, Refsnes M, Dybing E, and Schwarze PE. 2005. Cytokine release from alveolar macrophages exposed to ambient particulate matter: heterogeneity in relation to size, city and season. *Part Fibre Toxicol* 2:4.
- Heyder J. 2004. Deposition of inhaled particles in the human respiratory tract and consequences for regional targeting in respiratory drug delivery. *Proc Am Thorac Soc* 1:315–20.
- Heyder J, and Schulz H. 2005. Cardiovascular responses in unrestrained WKY rats to inhaled ultrafine carbon particles. *Inhal Toxicol* 17:29–42.

- Hidy GM, Lachenmyer C, Chow J, and Watson J. 2000. Urban outdoor–indoor PM_{2.5} concentrations and personal exposure in the Deep South. Part II. Inorganic chemistry. *Aerosol Sci Tech* 33:357–75.
- Hill LB, Zimmerman NJ, and Gooch J. 2005. A Multi-City Investigation of the Effectiveness of Retrofit Emissions Controls in Reducing Exposures to Particulate Matter in School Buses. Michigan, Clean Air Task Force.
- Hinds WC. 1999. *Aerosol Technology: Properties, Behavior, and Measurement of Airborne Particles*. 2nd edition. New York, NY: John Wiley & Sons.
- Hinwood AL, De Klerk N, Rodriguez C, Jacoby P, Runnion T, Rye P, Landau L, Murray F, Feldwick M, and Spickett J. 2006. The relationship between changes in daily air pollution and hospitalizations in Perth, Australia 1992–1998: A case-crossover study. *Int J Environ Health Res* 16:27–46.
- Hofmann W and Asgharian B. 2003. The effect of lung structure on mucociliary clearance and particle retention in human and rat lungs. *Toxicol Sci* 73:448–56.
- Hofmann W, Winkler-Heil R, and Balashazy I. 2006. The effect of morphological variability on surface deposition densities of inhaled particles in human bronchial and acinar airways. *Inhal Toxicol* 18:809–19.
- Höhr D, Steinfartz Y, Schins RP, Knaapen AM, Martra G, Fubini B, and Borm PJ. 2002. The surface area rather than the surface coating determines the acute inflammatory response after instillation of fine and ultrafine TiO₂ in the rat. *Int J Hyg Environ Health* 205:239–44.
- Holgate ST, Devlin RB, Wilson SJ, and Frew AJ. 2003. Health effects of acute exposure to air pollution. Part II: Healthy subjects exposed to concentrated ambient particles. *Res Rep Health Eff Inst* 112:31–50; disc. 51–67.
- Holguin F, Tellez-Rojo MM, Hernandez M, Cortez M, Chow JC, Watson JG, Mannino D, and Romieu I. 2003. Air pollution and heart rate variability among the elderly in Mexico City. *Epidemiology* 14:521–7.
- Hollingsworth JW 2nd, Cook DN, Brass DM, Walker JK, Morgan DL, Foster WM, and Schwartz DA. 2004. The role of Toll-like receptor 4 in environmental airway injury in mice. *Am J Respir Crit Care Med* 170:126–32.
- Holloman CH, Bortnick SM, Morara M, Strauss WJ, and Calder CA. 2004. A Bayesian hierarchical approach for relating PM_{2.5} exposure to cardiovascular mortality in North Carolina. *Environ Health Perspect* 112:1282–8.
- Hopke P and Markowitz D. 2002. A survey of monitoring instruments for measurement of airborne pollutants. New York State Energy Research and Development Authority. Report No. 03-05.
- Hopke PK, Ramadan Z, Paatero P, Norris GA, Landis MS, Williams RW, and Lewis CW. 2003. Receptor modeling of ambient and personal exposure samples: 1998 Baltimore Particulate Matter Epidemiology–Exposure Study. *Atmos Env* 37:3289–302.
- Hopke PK, Ito K, Mar T, Christensen WF, Eatough DJ, Henry RC, Kim E, Laden F, Lall R, Larson TV, Liu H, Neas L, Pinto J, Stölzel M, Suh H, Paatero P, and Thurston GD. 2006. PM source apportionment and health effects: 1. Intercomparison of source apportionment results. *J Expo Analysis Environ Epidemiol* 16:275–86.

- Hosseinpoor AR, Forouzanfar MH, Yunesian M, Asghari F, Naieni KH, and Farhood D. 2005. Air pollution and hospitalization due to angina pectoris in Tehran, Iran: a time-series study. *Environ Res* 99:126–31.
- Howard-Reed C, Rea AW, Zufall MJ, Burke JM, Williams RW, Suggs JC, Sheldon LS, Walsh D, and Kwok R. 2000. Use of a continuous nephelometer to measure personal exposure to particles during the U.S. Environmental Protection Agency Baltimore and Fresno panel studies. *J Air Waste Man Assoc* 50:1125–32.
- Howard-Reed C, Wallace LA, and Emmerich SJ. 2003. Effect of ventilation systems and air filters on decay rates of particles produced by indoor sources in an occupied townhouse. *Atmos Env* 37:5295–306.
- Huang SL, Hsu MK, and Chan CC. 2003a. Effects of submicrometer particle compositions on cytokine production and lipid peroxidation of human bronchial epithelial cells. *Environ Health Perspect* 111:478–82.
- Huang YC, Soukup J, Harder S, and Becker S. 2003b. Mitochondrial oxidant production by a pollutant dust and NO-mediated apoptosis in human alveolar macrophage. *Am J Physiol Cell Physiol* 284:C24–32.
- Huang YC, Ghio AJ, Stonehuerner J, McGee J, Carter JD, Grambow SC, and Devlin RB. 2003c. The role of soluble components in ambient fine particles-induced changes in human lungs and blood. *Inhal Toxicol* 15:327–42.
- Huang XF, Yu JZ, He L.Y., and Hu M. 2006. Size distribution characteristics of elemental carbon emitted from Chinese vehicles: results of a tunnel study and atmospheric implications. *Environ Sci Technol* 40:5355–60.
- Hussein T, Hämeri K, Aalto P, Asmi A, Kakko L, and Kulmala M. 2004. Particle size characterization and the indoor-to-outdoor relationship of atmospheric aerosols in Helsinki. *Scand J Work Env Health* 30 (Suppl. 2):54–62.
- Hussein T, Hämeri K, Heikkinen MSA, and Kulmala M. 2005. Indoor and outdoor particle size characterization at a family house in Espoo, Finland. *Atmos Env* 39:3697–709.
- Huynh M, Woodruff TJ, Parker JD, and Schoendorf KC. 2006. Relationships between air pollution and preterm birth in California. *Paediatr Perinat Epidemiol* 20(6): 454–61.
- Hwang BF, Lee YL, Lin YC, Jaakkola JJ, and Guo, Y L. 2005. Traffic related air pollution as a determinant of asthma among Taiwanese school children. *Thorax* 60:467–73.
- Hwang JS, Nadziejko C, and Chen LC. 2005. Effects of subchronic exposures to concentrated ambient particles (CAPs) in mice. III. Acute and chronic effects of CAPs on heart rate, heart-rate fluctuation, and body temperature. *Inhal Toxicol* 17:199–207.
- Hwang BF, Jaakkola JJ, Lee YL, Lin YC, and Guo YL. 2006. Relation between air pollution and allergic rhinitis in Taiwanese schoolchildren. *Respir Res* 7:23.
- Hwang JS and Chan CC. 2002. Effects of air pollution on daily clinic visits for lower respiratory tract illness. *Am J Epidemiol* 155:1–10.
- Hwang J-S, Hu T-H, and Chan C-C. 2004. Air pollution mix and emergency room visits for respiratory and cardiac diseases in Taipei. *J Data Sci* 2:311–27.
- Ibald-Mulli A, Timonen KL, Peters A, Heinrich J, Wolke G, Lanki T, Buzorius G, Kreyling WG, de Hartog J, Hoek G, ten Brink HM, and Pekkanen J. 2004. Effects of particulate air pollution on blood pressure and heart rate in subjects with cardiovascular disease: a multicenter approach. *Environ Health Perspect* 112:369–77.

- Inoue K, Takano H, Yanagisawa R, Sakurai M, Ichinose T, Sadakane K, and Yoshikawa T. 2005. Effects of nano particles on antigen-related airway inflammation in mice. *Respir Res* 6:106–117.
- Inoue K, Takano H, Yanagisawa R, Hirano S, Sakurai M, Shimada A, and Yoshikawa T. 2006a. Effects of airway exposure to nanoparticles on lung inflammation induced by bacterial endotoxin in mice. *Environ Health Perspect* 114:1325–30.
- Inoue K, Takano H, Yanagisawa R, Ichinose T, Sakurai M, and Yoshikawa T. 2006b. Effects of nano particles on cytokine expression in murine lung in the absence or presence of allergen. *Arch Toxicol* 80:614–19.
- Inoue KI, Takano H, Yanagisawa R, Hirano S, Kobayashi T, Ichinose T, and Yoshikawa T. 2006c. Effects of organic chemicals derived from ambient particulate matter on lung inflammation related to lipopolysaccharide. *Arch Toxicol* 80:833–8.
- International Commission on Radiation Protection (ICRP), Task Group of Committee 2. 1994. *Human Respiratory Tract Model for Radiological Protection*. New York: Pergamon Press.
- Isaacs KK and Martonen TB. 2005. Particle deposition in children's lungs: theory and experiment. *J Aerosol Med* 18:337–53.
- Ishii H, Fujii T, Hogg JC, Hayashi S, Mukae H, Vincent R, and van Eeden SF. 2004. Contribution of IL-1 beta and TNF-alpha to the initiation of the peripheral lung response to atmospheric particulates (PM₁₀). *Am J Physiol Lung Cell Mol Physiol* 287:L176–83.
- Ito K, Christensen WF, Eatough DJ, Henry RC, Kim E, Laden F, Lall R, Larson TV, Neas L, Hopke PK, and Thurston GD. 2006. PM source apportionment and health effects: 2. An investigation of intermethod variability in associations between source-apportioned fine particle mass and daily mortality in Washington, DC. *J Expo Sci Environ Epidemiol* 16:300–10.
- Iwai K, Mizuno S, Miyasaka Y, and Mori T. 2005. Correlation between suspended particles in the environmental air and causes of disease among inhabitants: cross-sectional studies using the vital statistics and air pollution data in Japan. *Environ Res* 99:106–17.
- Jaffe DH, Singer ME, and Rimm, AA. 2003. Air pollution and emergency department visits for asthma among Ohio Medicaid recipients, 1991-1996. *Environ Res* 91:21–8.
- Jalaludin BB, O'Toole BI, and Leeder SR. 2004. Acute effects of urban ambient air pollution on respiratory symptoms, asthma medication use, and doctor visits for asthma in a cohort of Australian children. *Environ Res* 95:32–42.
- Jalaludin B, Morgan G, Lincoln D, Sheppard V, Simpson R, and Corbett S. 2006. Associations between ambient air pollution and daily emergency department visits for cardiovascular disease in the elderly (65+ years), Sydney, Australia. *J Expos Anal Env Epidemiol* 16:225–37.
- Jalava PI, Salonen RO, Halinen AI, Penttinen P, Pennanen AS, Sillanpaa M, Sandell E, Hillamo R, and Hirvonen MR. 2006. *In vitro* inflammatory and cytotoxic effects of size-segregated particulate samples collected during long-range transport of wildfire smoke to Helsinki. *Toxicol Appl Pharmacol* 215:341–53.
- Jansen KL, Larson TV, Koenig JQ, Mar TF, Fields C, Stewart J, and Lippmann M. 2005. Associations between health effects and particulate matter and black carbon in subjects with respiratory disease. *Environ Health Perspect* 113:1741–6.
- Janssen NA, Hoek G, Brunekreef B, Harssema H, Mensink I, and Zuidhof A. 1998. Personal sampling of particles in adults: relation among personal, indoor, and outdoor air concentrations. *Am J Epidemiol* 147:537–47.

- Janssen NA, Hoek G, Harssema H, and Brunekreef B. 1999a. Personal exposure to fine particles in children correlates closely with ambient fine particles. *Arch Environ Health* 54:95–101.
- Janssen NA, Hoek G, Brunekreef B, and Harssema H. 1999b. Mass concentration and elemental composition of PM₁₀ in classrooms. *Occup Environ Med* 56:482–7.
- Janssen NA, Brunekreef B, van Vliet P, Aarts F, Meliefste K, Harssema H, and Fischer P. 2003. The relationship between air pollution from heavy traffic and allergic sensitization, bronchial hyperresponsiveness, and respiratory symptoms in Dutch schoolchildren. *Environ Health Perspect* 111:1512–18.
- Janssen NAH, Hoek G, Harssema H, and Brunekreef B. 1997. Childhood exposure to PM₁₀: relation between personal, classroom, and outdoor concentrations. *Occup Environ Med* 54:888–94.
- Janssen NAH, de Hartog JJ, Hoek G, Brunekreef B, Lanki T, Timonen KL, and Pekkanen J. 2000. Personal exposure to fine particulate matter in elderly subjects: relation between personal, indoor, and outdoor concentrations. *J Air Waste Man Assoc* 50:1133–43.
- Janssen NAH, Schwartz J, Zanobetti A, and Suh HH. 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* 110:43–9.
- Janssen NAH, Lanki T, Hoek G, Vallius M, de Hartog JJ, Van Grieken R, Pekkanen J, and Brunekreef B. 2005. Associations between ambient, personal, and indoor exposure to fine particulate matter constituents in Dutch and Finnish panels of cardiovascular patients. *Occup Environ Med* 62:868–77.
- Jantunen M, Hänninen O, Koistinen K, and Hashim JH. 2002. Fine PM measurements: personal and indoor air monitoring. *Chemosphere* 49:993–1007.
- Jedrychowski W, Bendkowska I, Flak E, Penar A, Jacek R, Kaim I, Spengler JD, Camann D, and Perera FP. 2004. Estimated risk for altered fetal growth resulting from exposure to fine particles during pregnancy: an epidemiologic prospective cohort study in Poland. *Environ Health Perspect* 112:1398–1402.
- Jerrett M, Burnett RT, Brook J, Kanaroglou P, Giovis C, Finkelstein N, and Hutchison B. 2004. Do socioeconomic characteristics modify the short term association between air pollution and mortality? Evidence from a zonal time series in Hamilton, Canada. *J Epidemiol Commun Health* 58:31–40.
- Jerrett M, Buzzelli M, Burnett RT, and DeLuca PF. 2005a. Particulate air pollution, social confounders, and mortality in small areas of an industrial city. *Soc Sci Med* 60:2845–63.
- Jerrett M, Burnett RT, Ma R, Pope CA 3rd, Krewski D, and Newbold KB. 2005b. Spatial analysis of air pollution and mortality in Los Angeles. *Epidemiology* 16:727–36.
- Jiménez LA, Drost EM, Gilmour PS, Rahman I, Antonicelli F, Ritchie H, MacNee W, and Donaldson K. 2002. PM(10)-exposed macrophages stimulate a proinflammatory response in lung epithelial cells via TNF-alpha. *Am J Physiol Lung Cell Mol Physiol* 282:L237–48.
- Johnson T, McCoy M, Capel J, Wijnberg L, and Ollison W. 1993. A comparison of ten time/activity databases. Effects of geographic location, temperature, demographic group and diary recall method. *In* Vostal JJ (Ed.). *Tropospheric ozone: nonattainment and design value issues*. Proceedings of an International Specialty Conference, Boston, October 27– 30, 1992. Pittsburg, PA: Air and Waste Management Association.

- Johnston FH, Webby RJ, Pilotto LS, Bailie RS, Parry DL, and Halpin SJ. 2006. Vegetation fires, particulate air pollution and asthma: a panel study in the Australian monsoon tropics. *Int J Environ Health Res* 16:391–404.
- Johnstone A, Uddin M, Pollard A, Heenan A, and Finlay WH. 2004. The flow inside an idealized form of the human extrathoracic airway. *Exper Fluids* 37: 673–89.
- Judek S, Jessiman B, and Stieb D. 2004. Estimated number of excess deaths in Canada due to air pollution. Unpublished document dated August 30, 2004, from Air Health Effects Division, Health Canada. Available at <http://www.metrovancouver.org/about/publications/Publications/AirPollutionDeaths.pdf>
- Kaan PM and Hegele RG. 2003. Interaction between respiratory syncytial virus and particulate matter in guinea pig alveolar macrophages. *Am J Respir Cell Mol Biol* 28:697–704.
- Kadiiska MB, Ghio AJ, and Mason RP. 2004. ESR investigation of the oxidative damage in lungs caused by asbestos and air pollution particles. *Spectrochim Acta A Mol Biomol Spectrosc* 60:1371–7.
- Kan H and Chen B. 2003a. Air pollution and daily mortality in Shanghai: a time-series study. *Arch Environ Health* 58:360–7.
- Kan H and Chen B. 2003b. A case-crossover analysis of air pollution and daily mortality in Shanghai. *J Occup Health* 45:119–24.
- Kan H, Jia J, and Chen B. 2003. Acute stroke mortality and air pollution: new evidence from Shanghai, China. *J Occup Health* 45:321–3.
- Kan HD, Chen BH, Fu CW, Yu SZ, and Mu LN. 2005. Relationship between ambient air pollution and daily mortality of SARS in Beijing. *Biomed Environ Sci* 18:1–4.
- Kang YJ, Li Y, Zhou Z, Roberts AM, Cai L, Myers SR, Wang L, and Schuchke DA. 2002. Elevation of serum endothelins and cardiotoxicity induced by particulate matter (PM_{2.5}) in rats with acute myocardial infarction. *Cardiovasc Toxicol* 2:253–61.
- Kapp N, Kreyling W, Schulz H, Im Hof V, Gehr P, Semmler M, and Geiser M. 2004. Electron energy loss spectroscopy for analysis of inhaled ultrafine particles in rat lungs. *Microsc Res Tech* 63:298–305.
- Karakatsani A, Andreadaki S, Katsouyanni K, Dimitroulis I, Trichopoulos D, and Benetou V. 2003. Air pollution in relation to manifestations of chronic pulmonary disease: a nested case-control study in Athens, Greece. *Euro J Epidemiol* 18:45–53.
- Karlsson HL, Nygren J, and Moller L. 2004. Genotoxicity of airborne particulate matter: the role of cell-particle interaction and of substances with adduct-forming and oxidizing capacity. *Mutat Res* 565:1–10.
- Karr C, Lumley T, Shepherd K, Davis R, Larson T, Ritz B, and Kaufman J. 2006. A case-crossover study of wintertime ambient air pollution and infant bronchiolitis. *Environ Health Perspect* 114:277–81.
- Karthikeyan S, Balasubramanian R, and Iouri K. 2006. Particulate air pollution from bushfires: Human exposure and possible health effects. *J Tox Environ Health A* 69:1895–1908.
- Kasamatsu J, Shima M, Yamazaki S, Tamura K, and Sun G. 2006. Effects of winter air pollution on pulmonary function of school children in Shenyang, China. *Int J Hyg Environ Health* 209:435–44.

- Kaur S, Nieuwenhuijsen M, and Colvile R. 2005a. Personal exposure of street canyon intersection users to PM_{2.5}, ultrafine particle counts and carbon monoxide in Central London, UK. *Atmos Env* 39:3629–41.
- Kawanaka Y, Matsumoto E, Wang N, Tsuchiya Y, Yun S-J, Jiang ZW, and Sakamoto K. 2006. Mutagenic activity of atmospheric ultrafine particles at a roadside site and a suburban site. *J Health Sci* 52:352–7.
- Keeler GJ, Dvonch T, Yip FY, Parker EA, Isreal BA, Marsik FJ, Morishita M, Barres JA, Robins TG, Brakefield-Caldwell W, and Sam M. 2002. Assessment of personal and community-level exposures to particulate matter among children with asthma in Detroit, Michigan, as part of Community Action Against Asthma (CAAA). *Environ Health Perspect* 110:173–81.
- Kelly JT and Asgharian B. 2003. Nasal molds as predictors of fine and coarse particle deposition in rat nasal airways. *Inhal Toxicol* 15:859–75.
- Kelly JT, Asgharian B, Kimbell JS, and Wong BA. 2004a. Particle deposition in human nasal airway replicas manufactured by different methods. Part I: Inertial regime particles. *Aerosol Sci Tech* 38:1063–71.
- Kelly JT, Asgharian B, Kimbell JS, and Wong BA. 2004b. Particle deposition in human nasal airway replicas manufactured by different methods. Part II: Ultrafine particles. *Aerosol Sci Tech* 38:1072–9.
- Khandoga A, Stampfl A, Takenaka S, Schulz H, Radykewicz R, Kreyling W, and Krombach F. 2004. Ultrafine particles exert prothrombotic but not inflammatory effects on the hepatic microcirculation in healthy mice *in vivo*. *Circulation* 109:1320–5.
- Kim CS and Jaques PA. 2004. Analysis of total respiratory deposition of inhaled ultrafine particles in adult subjects as various breathing patterns. *Aerosol Sci Tech* 38:525–40.
- Kim H, Lee JT, Hng YC, and Yoonsang Kim SMY. 2004. Evaluating the effect of daily PM₁₀ variation on mortality. *Inhal Toxicol* 16(s1): 55–8.
- Kim JH, Lim DH, Kim JK, Jeong SJ, and Son BK. 2005. Effects of particulate matter (PM₁₀) on the pulmonary function of middle-school children. *J Korean Med Sci* 20:42–5.
- Kim CS and Jaques PA. 2005. Total lung deposition of ultrafine particles in elderly subjects during controlled breathing. *Inhal Toxicol* 17:387–99.
- Kim D, Sass-Kortsak A, Purdham JP, Dales RE, and Brook JR. 2005. Sources of personal exposure to fine particles in Toronto, Ontario, Canada. *J Air Waste Man Assoc* 55:1134–46.
- Kim YM, Reed W, Lenz AG, Jaspers I, Silbajoris R, Nick HS, and Samet JM. 2005. Ultrafine carbon particles induce interleukin-8 gene transcription and p38 MAPK activation in normal human bronchial epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 288:L432–41.
- Kim J and Yang HE. 2005. Generalized additive model of air pollution to daily mortality. *Key Eng Mater* 277-279:487–91.
- Kim D, Sass-Kortsak A, Purdham JT, Dales RE, and Brook JR. 2006. Associations between personal exposures and fixed-site ambient measurements of fine particulate matter, nitrogen dioxide, and carbon monoxide in Toronto, Canada. *J Expo Analysis Environ Epidemiol* 16:172–83.
- Kim JS, Yoon TJ, Yu KN, Kim BG, Park SJ, Kim HW, Lee KH, Park SB, Lee JK, and Cho MH. 2006. Toxicity and tissue distribution of magnetic nanoparticles in mice. *Toxicol Sci* 89:338–47.

- Kinney PL, Chillrud SN, Ramstrom S, Ross J, and Spengler JD. 2002. Exposures to multiple air toxics in New York City. *Environ Health Perspect* 110:539–46.
- Kittelsohn DB. 1998. Engines and nanoparticles: a review. *J Aerosol Sci* 29:575–88.
- Kleinman MT, Hamade A, Meacher D, Oldham M, Sioutas C, Chakrabarti B, Stram D, Froines JR, and Cho AK. 2005. Inhalation of concentrated ambient particulate matter near a heavily trafficked road stimulates antigen-induced airway responses in mice. *J Air Waste Manag Assoc* 55:1277–88.
- Kleinman MT, Hyde DM, Bufalino C, Basbaum C, Bhalla DK, and Mautz WJ. 2003. Toxicity of chemical components of fine particles inhaled by aged rats: effects of concentration. *J Air Waste Manag Assoc* 53:1080–7.
- Klein-Patel ME, Diamond G, Boniotto M, Saad S, and Ryan LK. 2006. Inhibition of beta-defensin gene expression in airway epithelial cells by low doses of residual oil fly ash is mediated by vanadium. *Toxicol Sci* 92:115–25.
- Klemm RJ, Lipfert FW, Wyzga RE, and Gust C. 2004. Daily mortality and air pollution in Atlanta: two years of data from ARIES. *Inhal Tox* 16 Suppl 1:131–41.
- Klepeis NE, Nelson WC, Ott WR, Robinson JP, Tsang AM, Switzer P, Behar JV, Hern SC, and Engelmann WH. 2001. The National Human Activity Pattern Survey (NHAPS): a resource for assessing exposure to environmental pollutants. *J Expo Analysis Environ Epidemiol* 11:231–52.
- Knaapen AM, Shi T, Borm PJ, and Schins RP. 2002. Soluble metals as well as the insoluble particle fraction are involved in cellular DNA damage induced by particulate matter. *Mol Cell Biochem* 234–235:317–26.
- Knaapen AM, Borm PJ, Albrecht C, and Schins RP. 2004. Inhaled particles and lung cancer. Part A: Mechanisms. *Int J Cancer* 109:799–809.
- Kocbach A, Li Y, Yttri KE, Cassee FR, Schwarze PE, and Namork E. 2006. Physicochemical characterization of combustion particles from vehicle exhaust and residential wood smoke. Part I. *Fibr Tox* 3:1–10.
- Kodavanti UP, Moyer CF, Ledbetter AD, Schladweiler MC, Costa DL, Hauser R, Christiani DC, and Nyska A. 2003. Inhaled environmental combustion particles cause myocardial injury in the Wistar Kyoto rat. *Toxicol Sci* 71:237–45.
- Kodavanti UP, Schladweiler MC, Ledbetter AD, McGee JK, Walsh L, Gilmour PS, Highfill JW, Davies D, Pinkerton KE, Richards JH, Crissman K, Andrews D, and Costa DL. 2005. Consistent pulmonary and systemic responses from inhalation of fine concentrated ambient particles: roles of rat strains used and physicochemical properties. *Environ Health Perspect* 113:1561–8.
- Koenig JQ, Jansen K, Mar TF, Lumley T, Kaufman J, Trenga CA, Sullivan J, Liu LJ, Shapiro GG, and Larson TV. 2003. Measurement of offline exhaled nitric oxide in a study of community exposure to air pollution. *Environ Health Perspect* 111:1625–9.
- Koenig JQ, Mar TF, Allen RW, Jansen K, Lumley T, Sullivan JH, Trenga CA, Larson T, and Liu LJ. 2005. Pulmonary effects of indoor- and outdoor-generated particles in children with asthma. *Environ Health Perspect* 113:243–9.
- Koike E and Kobayashi T. 2006. Chemical and biological oxidative effects of carbon black nanoparticles. *Chemosphere* 65:946–51.
- Koistinen KJ, Hänninen O, Rotko T, Edwards RD, Moschandreas D, and Jantunen MJ. 2001. Behavioral and environmental determinants of personal exposures to PM_{2.5} in EXPOLIS—Helsinki, Finland. *Atmos Env* 35:2473–81.

Koistinen KJ, Edwards RD, Mathys P, Ruuskanen J, Künzli N, and Jantunen MJ. 2004. Sources of fine particulate matter in personal exposures and residential indoor, residential outdoor and workplace microenvironments in the Helsinki phase of the EXPOLIS study. *Scand J Work Env Health* 30 (Suppl. 2):36–46.

Kojic M and Tsuda A. 2004. A simple model for gravitational deposition of non-diffusing particles in oscillatory laminar pipe flow and its application to small airways. *J Aerosol Sci* 2:245–61.

Koken PJ, Piver WT, Ye F, Elixhauser A, Olsen LM, and Portier CJ. 2003. Temperature, air pollution, and hospitalization for cardiovascular diseases among elderly people in Denver. *Environ Health Perspect* 111:1312–17.

Kongtip P, Thongsuk W, Yoosook W, and Chantanakul S. 2006. Health effects of metropolitan traffic-related air pollutants on street vendors. *Atmos Environ* 40(37):7138–7145.

Kooter I, Pennings J, Opperhuizen A, and Cassee F. 2005. Gene expression pattern in spontaneously hypertensive rats exposed to urban particulate matter (EHC-93). *Inhal Toxicol* 17:53–65.

Kooter IM, Boere AJ, Fokkens PH, Leseman DL, Dormans JA, and Cassee FR. 2006. Response of spontaneously hypertensive rats to inhalation of fine and ultrafine particles from traffic: experimental controlled study. Part Fibre Toxicol 3:7.

Koponen IK, Asmi A, Keronen P, Puhto K, and Kulmala M. 2001. Indoor air measurement campaign in Helsinki, Finland 1999—the effect of outdoor air pollution on indoor air. *Atmos Env* 35:1465–1477.

Kopperud RJ, Ferro AR, and Hildemann LM. 2004. Outdoor versus indoor contributions to indoor particulate matter (PM) determined by mass balance methods. *J Air Waste Man Assoc* 54:1188–96.

Kousa A, Oglesby L, Koistinen K, Künzli N, and Jantunen M. 2002. Exposure chain of urban air PM_{2.5}—associations between ambient fixed site, residential outdoor, indoor, workplace and personal exposures in four European cities in the EXPOLIS study. *Atmos Env* 36:3031–9.

Koutrakis P and Briggs SLK. 1992. Source apportionment of indoor aerosols in Suffolk and Onondaga counties, New York. *Environ Sci Technol* 26:521–7.

Koutrakis P, Suh H H, Sarnat J A, Brown KW, Coull B A, and Schwartz J. 2005. Characterization of Particulate and Gas Exposures of Sensitive Subpopulations Living in Baltimore and Boston. Boston, MA: Health Effects Institute. Research Report No. 131.

Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, Abramowicz M, and White WH. 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.

Krewski D, Burnett R, Jerrett M, Pope CA, Rainham D, and Calle E. 2005. Mortality and long-term exposure to ambient air pollution: ongoing analyses based on the American Cancer Society cohort. *J Toxicol Environ Health A* 68:1093–1109.

Kreyling WG, Semmler M, and Moller W. 2004. Dosimetry and toxicology of ultrafine particles. *J Aerosol Med* 17:140–52.

Kristovich R, Knight DA, Long JF, Williams MV, Dutta PK, and Waldman WJ. 2004. Macrophage-mediated endothelial inflammatory responses to airborne particulates: impact of particulate physicochemical properties. *Chem Res Toxicol* 17:1303–12.

- Kuempel, ED, Tran CL, Castranova V, and Bailer AJ. 2006. Lung dosimetry and risk assessment of nanoparticles: evaluating and extending current models in rats and humans. *Inhal Toxicol* 18:717–24.
- Kuhn T, Krudysz M, Zhu Y, Hinds WC, Froines J, Fine PM, and Sioutas C. 2005. Volatility of indoor and outdoor ultrafine particulate matter near a freeway. *J Aerosol Sci* 36:291–302.
- Kulkarni N, Pierse N, Rushton L, and Grigg J. 2006. Carbon in airway macrophages and lung function in children. *N Engl J Med* 355:21–30.
- Kulmala M, Asmia A, and Pirjola I. 1999. Indoor air aerosol model: the effect of outdoor air, filtration and ventilation on indoor concentrations. *Atmos Env* 33:2133–44.
- Kumarathasan P, Blais E, Goegan P, Yagminas A, Guenette J, Adamson IY, Crapo JD, Mason RJ, and Vincent R. 2005. 90-day repeated inhalation exposure of surfactant Protein-C/tumor necrosis factor-alpha, (SP-C/TNF-alpha) transgenic mice to air pollutants. *Int J Toxicol* 24:59–67.
- Kunzli N, Jerrett M, Mack WJ, Beckerman B, LaBree L, Gilliland F, Thomas D, Peters J, and Hodis HN. 2005. Ambient air pollution and atherosclerosis in Los Angeles. *Environ Health Perspect* 113:201–6.
- Kuo CY, Hsu YW, and Lee HS. 2003. Study of human exposure to particulate PAHs using personal air samplers. *Arch Environ Con Tox* 44:454–9.
- Kuo HW, Lai JS, Lee MC, Tai RC, and Lee MC. 2002. Respiratory effects of air pollutants among asthmatics in central Taiwan. *Arch Environ Health* 57:194–200.
- Kwon HJ, Cho SH, Chun Y, Lagarde F, and Pershagen G. 2002. Effects of the Asian dust events on daily mortality in Seoul, Korea. *Environ Res* 90:1–5.
- Lacasana M, Esplugues A, and Ballester F. 2005. Exposure to ambient air pollution and prenatal and early childhood health effects. *Eur J Epidemiol* 20:183–99.
- Lachenmyer C and Hidy GM. 2000. Urban measurements of outdoor–indoor PM_{2.5} concentrations and personal exposure in the deep south. Part I. Pilot study of mass concentrations for nonsmoking subjects. *Aerosol Sci Tech* 32:34–51.
- Laden F, Schwartz J, Speizer FE, and Dockery DW. 2006. Reduction in fine particulate air pollution and mortality: extended follow-up of the Harvard Six Cities Study. *Am J Respir Crit Care Med* 173:667–72.
- Lagorio S, Forastiere F, Pistelli R, Iavarone I, Michelozzi P, Fano V, Marconi A, Ziemacki G, and Ostro BD. 2006. Air pollution and lung function among susceptible adult subjects: a panel study. *Environ Health* 5:11.
- Lai ACK, Byrne MA, and Goddard AJH. 1999. Measured deposition of aerosol particles on a two-dimensional ribbed surface in a turbulent duct flow. *J Aerosol Sci* 30:1201–14.
- Lai ACK. Particle deposition indoors: a review. 2002. *Indoor Air* 12:211–14.
- Lai HK, Kendall M, Ferrier H, Lindup I, Alm S, Hänninen O, Jantunen M, Mathys P, Colville R, Ashmore MR, Cullinan P, and Nieuwenhuijsen MJ. 2004. Personal exposures and microenvironment concentrations of PM_{2.5}, VOC, NO₂ and CO in Oxford, UK. *Atmos Env* 38:6399–410.
- Lambert AL, Mangum JB, DeLorme MP, and Everitt JI. 2003a. Ultrafine carbon black particles enhance respiratory syncytial virus-induced airway reactivity, pulmonary inflammation, and chemokine expression. *Toxicol Sci* 72:339–46.

- Lambert AL, Trasti FS, Mangum JB, and Everitt JI. 2003b. Effect of preexposure to ultrafine carbon black on respiratory syncytial virus infection in mice. *Toxicol Sci* 72:331–8.
- Landis MS, Norris GA, Williams RW, and Weinstein JP. 2001. Personal exposures to PM_{2.5} mass and trace elements in Baltimore, MD, USA. *Atmos Env* 35:6511–24.
- Lanki T, Alm S, Ruuskanen J, Janssen NA, Jantunen M, and Pekkanen J. 2002. Photometrically measured continuous personal PM (2.5) exposure: levels and correlation to a gravimetric method. *J Expo Analysis Environ Epidemiol* 12:172–8.
- Lanki T, Pekkanen J, Aalto P, Elosua R, Berglind N, D'ippoliti D, Kulmala M, Nyberg F, Peters A, Picciotto S, Salomaa V, Sunyer J, Tiittanen P, Von Klot S, and Forastiere F. 2006a. Associations of traffic-related air pollutants with hospitalisation for first acute myocardial infarction. The HEAPSS study. *Occup Environ Med* 63:844–51 (pre-published online in 2006).
- Lanki T, de Hartog JJ, Heinrich J, Hoek G, Janssen NA, Peters A, Stolzel M, Timonen KL, Vallius M, Vanninen E, and Pekkanen J. 2006b. Can we identify sources of fine particles responsible for exercise-induced ischemia on days with elevated air pollution? The ULTRA study. *Environ Health Perspect* 114:655–60.
- Larson T, Gould T, Simpson C, Liu LJS, Claiborn C, and Lewtas J. 2004. Source apportionment of indoor, outdoor, and personal PM_{2.5} in Seattle, Washington, using positive matrix factorization. *J Air Waste Man Assoc* 54:1175–87.
- Last JA, Ward R, Temple L, Pinkerton KE, and Kenyon NJ. 2004. Ovalbumin-induced airway inflammation and fibrosis in mice also exposed to ultrafine particles. *Inhal Toxicol* 16:93–102.
- Leaderer BP, Naeher L, Jankun T, Balenger K, Holford TR, Toth C, Sullivan J, Wolfson JM, and Koutrakis P. 1999. Indoor, outdoor, and regional summer and winter concentrations of PM₁₀, PM_{2.5}, SO₄²⁻, H⁺, NH₄⁺, NO₃⁻, NH₃, and nitrous acid in homes with and without kerosene space heaters. *Environ Health Perspect* 107:223–31.
- Lee BE, Ha EH, Park HS, Kim YJ, Hong YC, Kim H, and Lee JT. 2003. Exposure to air pollution during different gestational phases contributes to risks of low birth weight. *Hum Reprod* 18:638–43.
- Lee JT, Kim H, Cho YS, Hong YC, Ha EH, and Park H. 2003. Air pollution and hospital admissions for ischemic heart diseases among individuals 64+ years of age residing in Seoul, Korea. *Arch Environ Health* 58:617–23.
- Lee SL, Wong WHS, and Lau YL. 2006. Association between air pollution and asthma admission among children in Hong Kong. *Clin Exp Allergy* 36:1138–46.
- Leech J and Smith-Doiron M. 2006. Exposure time and place: Do COPD patients differ from the general population? *J Expo Sci Environ Epidemiol* 16:238–41.
- Leech JA, Nelson WC, Burnett RT, Aaron S, and Raizenne ME. 2002. It's about time: a comparison of Canadian and American time-activity patterns. *J Expo Analysis Environ Epidemiol* 12:427–32.
- Leech JL, Wilby K, McMullen E, and Laporte K. 1996. The Canadian human activity pattern survey: report of methods and population surveyed. *Chronic Dis Can* 17:118–23.
- Leem JH, Kaplan BM, Shim YK, Pohl HR, Gotway CA, Bullard SM, Rogers JF, Smith MM, and Tylenda CA. 2006. Exposures to air pollutants during pregnancy and preterm delivery. *Environ Health Perspect* 114:905–10.

- Lei YC, Chan CC, Wang PY, Lee CT, and Cheng TJ. 2004a. Effects of Asian dust event particles on inflammation markers in peripheral blood and bronchoalveolar lavage in pulmonary hypertensive rats. *Environ Res* 95:71–6.
- Lei YC, Chen MC, Chan CC, Wang PY, Lee CT, and Cheng TJ. 2004b. Effects of concentrated ambient particles on airway responsiveness and pulmonary inflammation in pulmonary hypertensive rats. *Inhal Toxicol* 16:785–92.
- Lei YC, Hwang JS, Chan CC, Lee CT, and Cheng TJ. 2005. Enhanced oxidative stress and endothelial dysfunction in streptozotocin-diabetic rats exposed to fine particles. *Environ Res* 99:335–43.
- Lemos M, Mohallen SV, Macchione M, Dolhnikoff M, Assunção J, Godleski JJ, and Saldiva PHN. 2006. Chronic exposure to urban air pollution induces structural alterations in murine pulmonary and coronary arteries. *Inhal Toxicol* 18:247–53.
- Lepeule J, Rondeau V, Filleul L, and Dartigues JF. 2006. Survival analysis to estimate association between short-term mortality and air pollution. *Environ Health Perspect* 114:242–7.
- Letz AG and Quinn JM. 2005. Relationship of basic military trainee emergency department visits for asthma and San Antonio Air Quality. *Allergy and Asthma Proc* 26:463–7.
- Levy JI, Dumyahn T, and Spengler JD. 2002. Particulate matter and polycyclic aromatic hydrocarbon concentrations in indoor and outdoor microenvironments in Boston, Massachusetts. *J Expo Analysis Environ Epidemiol* 12:104–14.
- Levy JI, Bennett DH, Melly SJ, and Spengler JD. 2003. Influence of traffic patterns on particulate matter and polycyclic aromatic hydrocarbon concentrations in Roxbury, Massachusetts. *J Expo Analysis Environ Epidemiol* 13:364–71.
- Lewis AB, Taylor MD, Roberts JR, Leonard SS, Shi X, and Antonini JM. 2003. Role of metal-induced reactive oxygen species generation in lung responses caused by residual oil fly ash. *J Biosci* 28:13–8.
- Lewis C, Norris GA, and Conner TL. 2003. Source apportionment of Phoenix PM_{2.5} Aerosol with the Unmix Receptor Model. *J Air Waste Man Assoc* 53:325–38.
- Lewis CW. 1991. Sources of air pollutants indoors: VOC and fine particulate species. *J Expo Analysis Environ Epidemiol* 1:31–44.
- Lewis TC, Robins TG, Dvonch JT, Keeler GJ, Yip FY, Mentz GB, Lin X, Parker EA, Israel BA, Gonzalez L, and Hill Y. 2005. Air pollution-associated changes in lung function among asthmatic children in Detroit. *Environ Health Perspect* 113:1068–75.
- Li N, Kim S, Wang M, Froines J, Sioutas C, and Nel A. 2002. Use of a stratified oxidative stress model to study the biological effects of ambient concentrated and diesel exhaust particulate matter. *Inhal Toxicol* 14:459–86.
- Li N, Sioutas C, Cho A, Schmitz D, Misra C, Sempf J, Wang M, Oberley T, Froines J, and Nel A. 2003. Ultrafine particulate pollutants induce oxidative stress and mitochondrial damage. *Environ Health Perspect* 111:455–60.
- Li Z, Hyseni X, Carter JD, Soukup JM, Dailey LA, and Huang Y-CT. 2006. Pollutant particles enhanced H₂O₂ production from NAD(P)H oxidase and mitochondria in human pulmonary artery endothelial cells. *Am J Physiol Cell Physiol* 291:C357–65.
- Liang CSK and Waldman JM. 1992. Indoor exposures to acidic aerosols at child and elderly care facilities. *Indoor Air* 2:196–207.

- Liao C-M, Huang S-J, and Yu H. 2004. Size-dependent particulate matter indoor/outdoor relationships for a wind-induced naturally ventilated airspace. *Build Environ* 39:411–20.
- Liao D, Duan Y, Whitsel EA, Zheng ZJ, Heiss G, Chinchilli VM, and Lin HM. 2004. Association of higher levels of ambient criteria pollutants with impaired cardiac autonomic control: a population-based study. *Am J Epidemiol* 159:768–77.
- Liao D, Heiss G, Chinchilli VM, Duan Y, Folsom AR, Lin HM, and Salomaa V. 2005. Association of criteria pollutants with plasma hemostatic/inflammatory markers: a population-based study. *J Expo Anal Environ Epidemiol* 15:319–28.
- Lierl MB and Hornung RW. 2003. Relationship of outdoor air quality to pediatric asthma exacerbations. *Ann Allergy Asthma Immunol* 90:28–33.
- Lin CA, Amador Pereira LA, De Souza Conceicao GM, Kishi HS, Milani R Jr, Ferreira Braga AL, and Nascimento Saldiva PH. 2003. Association between air pollution and ischemic cardiovascular emergency room visits. *Environ Res* 92:57–63.
- Lin CM, Li CY, Yang GY, and Mao IF. 2004. Association between maternal exposure to elevated ambient sulfur dioxide during pregnancy and term low birth weight. *Environ Res* 96:41–50.
- Lin M, Stieb DM, and Chen Y. 2005. Coarse particulate matter and hospitalization for respiratory infections in children younger than 15 years in Toronto: a case-crossover analysis. *Pediatrics* 116:e235–40.
- Linares C, Diaz J, Tobias A, Miguel JM, and Otero A. 2006. Impact of urban air pollutants and noise levels over daily hospital admissions in children in Madrid: a time series analysis. *Int Arch Occup Environ Health* 79:143–52.
- Linn WS, Gong HJr, Clark KW, and Anderson KR. 1999. Day-to-day particulate exposures and health changes in Los Angeles area residents with severe lung disease. *J Air Waste Man Assoc* 49:PM108–PM115.
- Lioy PJ, Waldman JM, Buckley T, Butler J, and Pietarinen C. 1990. Personal, indoor and outdoor concentrations of PM₁₀ measured in an industrial community during the winter. *Atmos Env B* 24:57–66.
- Lipfert FW, Baty JD, Miller J P, and Wyzga RE. 2006. PM_{2.5} constituents and related air quality variables as predictors of survival in a cohort of U. S. military veterans. *Inhal Toxicol* 18:645–57.
- Lippmann M, Hwang JS, Maciejczyk P, and Chen LC. 2005. PM source apportionment for short-term cardiac function changes in ApoE^{-/-} mice. *Environ Health Perspect* 113:1575–9.
- Lippmann M, Ito K, Hwang JS, Maciejczyk P, and Chen LC. 2006. Cardiovascular effects of nickel in ambient air. *Environ Health Perspect* 114:1662–9.
- Lipsett MJ, Tsai FC, Roger L, Woo M, and Ostro BD. 2006. Coarse particles and heart rate variability among older adults with coronary artery disease in the Coachella Valley, California. *Environ Health Perspect* 114:1215–20.
- Liu DL and Nazaroff WW. 2001. Modeling pollutant penetration across building envelopes. *Atmos Env* 35:4451–62.
- Liu L-JS, Box M, Kalman D, Kaufman J, Koenig J, Larson T, Lumley T, Sheppard L, and Wallace L. 2003. Exposure assessment of particulate matter for susceptible populations in Seattle. *Environ Health Perspect* 111:909–18.

- Liu S, Krewski D, Shi Y, Chen Y, and Burnett RT. 2003. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. *Environ Health Perspect* 111:1773–8.
- Liu S, Krewski D, Shi Y, Chen Y, and Burnett RT. 2007. Association between maternal exposure to ambient air pollutants during pregnancy and fetal growth restriction. *J Expo Sci Environ Epidemiol* 17:426–432 (pre-published online in 2006).
- Liu X and Meng Z. 2005. Effects of airborne fine particulate matter on antioxidant capacity and lipid peroxidation in multiple organs of rats. *Inhal Toxicol* 17:467–73.
- Llorca J, Salas A, Prieto-Salceda D, Chinchon-Bengoechea V, and Delgado-Rodriguez M. 2005. Nitrogen dioxide increases cardiorespiratory admissions in Torrelavega (Spain). *J Environ Health* 68:30–5.
- Long CM and Sarnat JA. 2004. Indoor–outdoor relationships and infiltration behavior of elemental components of outdoor PM_{2.5} for Boston-area homes. *Aerosol Sci Tech* 38 (Suppl. 2):91–104.
- Long CM, Suh HH, and Koutrakis P. 2000. Characterization of indoor particle sources using continuous mass and size monitors. *J Air Waste Man Assoc* 50:1236–50.
- Long CM, Suh HH, Catalano PJ, and Koutrakis P. 2001a. Using time- and size-resolved particulate data to quantify indoor penetration and deposition behavior. *Environ Sci Technol* 35:2089–99.
- Long CM, Suh HH, Kobzik L, Catalano PJ, Ning YY, and Koutrakis P. 2001b. 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* 109:1019–26.
- Longest PW and Oldham MJ. 2006. Mutual enhancements of CFD modeling and experimental data: a case study of 1- μ m particle deposition in a branching airway model. *Inhal Toxicol* 18:761–71.
- Low RB, Bielory L, Qureshi AI, Dunn V, Stuhlmiller DF, and Dickey DA. 2006. The relation of stroke admissions to recent weather, airborne allergens, air pollution, seasons, upper respiratory infections, and asthma incidence, September 11, 2001, and day of the week. *Stroke* 37:951–7.
- Lubinski W, Toczyska I, Chcialowski A, and Plusa T. 2005. Influence of air pollution on pulmonary function in healthy young men from different regions of Poland. *Ann Agric Environ Med* 12:1–4.
- Luginaah IN, Fung KY, Gorey KM, Webster G, and Wills C. 2005. Association of ambient air pollution with respiratory hospitalization in a government-designated "area of concern": the case of Windsor, Ontario. *Environ Health Perspect* 113:290–6.
- Lunden MM, Thatcher TL, Hering SV, and Brown NJ. 2003a. Use of time- and chemically resolved particulate data to characterize the infiltration of outdoor PM_{2.5} into a residence in the San Joaquin Valley. *Environ Sci Technol* 37:4724–32.
- Lunden MM, Revzan KL, Fischer ML, Thatcher TL, Littlejohn D, Hering SV, and Brown NJ. 2003b. The transformation of outdoor ammonium nitrate aerosols in the indoor environment. *Atmos Env* 37:5633–44.
- Luttmann-Gibson H, Suh HH, Coull BA, Dockery DW, Sarnat SE, Schwartz J, Stone PH, and Gold DR. 2006. Short-term effects of air pollution on heart rate variability in senior adults in Steubenville, Ohio. *J Occup Environ Med* 48:780–8.

- Lwebuga-Mukasa JS, Ayirookuzhi SJ, and Hyland A. 2003. Traffic volumes and respiratory health care utilization among residents in close proximity to the Peace Bridge before and after September 11, 2001. *J Asthma* 40:855–64.
- Maciejczyk P and Chen LC. 2005. Effects of subchronic exposures to concentrated ambient particles (CAPs) in mice. VIII. Source-related daily variations in *in vitro* responses to CAPs. *Inhal Toxicol* 17:243–53.
- Madsen C and Nafstad P. 2006. Associations between environmental exposure and blood pressure among participants in the Oslo Health Study (HUBRO). *Eur J Epidemiol* 21:485–91.
- Magari SR, Schwartz J, Williams PL, Hauser R, Smith TJ, and Christiani DC. 2002. The association of particulate air metal concentrations with heart rate variability. *Environ Health Perspect* 110:875–80.
- Mage D, Wilson W, Hasselblad V, and Grant L. 1999. Assessment of human exposure to ambient particulate matter. *J Air Waste Man Assoc* 49:1280–91.
- Maheswaran R, Haining RP, Brindley P, Law J, Pearson T, Fryers PR, Wise S, and Campbell MJ. 2005a. Outdoor air pollution and stroke in Sheffield, United Kingdom: a small-area level geographical study. *Stroke* 36:239–43.
- Maheswaran R, Haining RP, Brindley P, Law J, Pearson T, Fryers PR, Wise S, and Campbell MJ. 2005b. Outdoor air pollution, mortality, and hospital admissions from coronary heart disease in Sheffield, UK: a small-area level ecological study. *Eur Heart J* 26:2543–9.
- Mangum J, Bermudez E, Sar M, and Everitt J. 2004. Osteopontin expression in particle-induced lung disease. *Exp Lung Res* 30:585–98.
- Mann JK, Tager IB, Lurmann F, Segal M, Quesenberry CPJr, Lugg MM, Shan J, and Van Den Eeden SK. 2002. Air pollution and hospital admissions for ischemic heart disease in persons with congestive heart failure or arrhythmia. *Environ Health Perspect* 110:1247–52.
- Mannes T, Jalaludin B, Morgan G, Lincoln D, Sheppard V, and Corbett S. 2005. Impact of ambient air pollution on birth weight in Sydney, Australia. *Occup Environ Med* 62:524–30.
- Mar TF, Larson TV, Stier RA, Claiborn C, and Koenig JQ. 2004. An analysis of the association between respiratory symptoms in subjects with asthma and daily air pollution in Spokane, Washington. *Inhal Toxicol* 16:809–15.
- Mar TF, Koenig JQ, Jansen K, Sullivan J, Kaufman J, Trenga CA, Siahpush SH, Liu LJ, and Neas L. 2005a. Fine particulate air pollution and cardiorespiratory effects in the elderly. *Epidemiology* 16:681–7.
- Mar TF, Jansen K, Shepherd K, Lumley T, Larson TV, and Koenig JQ. 2005b. Exhaled nitric oxide in children with asthma and short-term PM_{2.5} exposure in Seattle. *Environ Health Perspect* 113:1791–4.
- Mar TF, Ito K, Koenig JQ, Larson TV, Eatough DJ, Henry RC, Kim E, Laden F, Lall R, Neas L, Stölzel M, Paatero P, Hopke PhK, and Thurston GD. 2006. PM source apportionment and health effects. 3. Investigation of inter-method variations in associations between estimated source contributions of PM_{2.5} and daily mortality in Phoenix, AZ. *J Expo Analysis Environ Epidemiol* 16:311–20.
- Martins LC, Latorre Mdo R, Saldiva PH, and Braga AL. 2002. Air pollution and emergency room visits due to chronic lower respiratory diseases in the elderly: an ecological time-series study in Sao Paulo, Brazil. *J Occup Environ Med* 44:622–7.

- Martins MC, Fatigati FL, Vespoli TC, Martins LC, Pereira LA, Martins MA, Saldiva PH, and Braga AL. 2004. Influence of socioeconomic conditions on air pollution adverse health effects in elderly people: an analysis of six regions in Sao Paulo, Brazil. *J Epidemiol Commun Health* 58:41–6.
- Martonen TB, Zhang Z, Yue G, and Musante CJ. 2003. Fine particle deposition within human nasal airways. *Inhal Toxicol* 15:283–303.
- Martonen T, Fleming J, Schreter J, Conway J, and Hwang D. 2003b. *In silico* modeling of asthma. *Advanced Drug Delivery Reviews*, 55: 829–49.
- Martonen T, Isaacs K, and Hwang D. 2005. Three-dimensional simulations of airways within human lungs. *Cell Biochem Biophys* 42:223–49.
- Martuzevicius D, Grinshpun SA, Reponen T, Gorny RL, Shukla R, Lockey J, Hu SH, McDonald R, Biswas P, Kliucininkas L, and LeMasters G. 2004. Spatial and temporal variations of PM_{2.5} concentration and composition throughout an urban area with high freeway density—the Greater Cincinnati study. *Atmos Env* 38:1091–1105.
- Massolo L, Muller A, Tueros M, Rehwagen M, Franck U, Ronco A, and Herbarth O. 2002. Assessment of mutagenicity and toxicity of different-size fractions of air particulates from La Plata, Argentina, and Leipzig, Germany. *Environ Toxicol* 17:219–31.
- McConnell R, Berhane K, Gilliland F, Molitor J, Thomas D, and Lurmann F. 2003. Prospective study of air pollution and bronchitic symptoms in children with asthma. *Am J Respir Crit Care Med* 68:790–7.
- McConnell R, Berhane K, Gilliland F, Molitor J, Gilliland F, Kunzli N, Thorne PS, Thomas D, Gauderman WJ, Avol E, Lurmann F, Rappaport E, Jerrett M, and Peters, JM. 2006. Dog ownership enhances symptomatic responses to air pollution in children with asthma. *Environ Health Perspect* 114:1910–15.
- McDonald JD, Eide I, Seagrave J, Zielinska B, Whitney K, Lawson DR, and Mauderly JL. 2004. Relationship between composition and toxicity of motor vehicle emission samples. *Environ Health Perspect* 112:1527–38.
- McDonnell WF, Nishino-Ishikawa N, Petersen, FF, Chen LH, and Abbey DE. 2000. Relationships of mortality with the fine and coarse fractions of long-term ambient PM₁₀ concentrations in nonsmokers. *J Expos Anal Environ Epidemiol* 10:427–36.
- Medeiros N Jr, Rivero DH, Kasahara DI, Saiki M, Godleski JJ, Koutrakis P, Capelozzi VL, Saldiva PH, and Antonangelo L. 2004. Acute pulmonary and hematological effects of two types of particle surrogates are influenced by their elemental composition. *Environ Res* 95:62–70.
- Medina-Ramon M, Zanobetti A, and Schwartz J. 2006. The Effect of ozone and PM₁₀ on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol* 163:579–88.
- Meng QY, Turpin BJ, Korn L, Weisel CP, Morandi M, Colome S, Zhang JFJ, Stock T, Spektor D, Winer A, Zhang L, Lee JH, Giovanetti R, Cui W, Kwon J, Alimokhtari S, Shendell D, Jones J, Farrar C, and Maberti S. 2005a. Influence of ambient (outdoor) sources on residential indoor and personal PM_{2.5} concentrations: Analyses of RIOPA data. *J Expo Analysis Environ Epidemiol* 15:17–28.
- Meng QY, Turpin BJ, Polidori A, Lee JH, Weisel C, Morandi M, Colome S, Stock T, Winer A, and Zhang J. 2005b. PM_{2.5} of ambient origin: estimates and exposure errors relevant to PM epidemiology. *Environ Sci Technol* 39:5105–12.

- Meng Z and Zhang Q. 2006. Oxidative damage of dust storm fine particles instillation on lungs, hearts and livers of rats. *Environ Toxicol Pharmacol* 22:277–82.
- Merolla L and Richards RJ. 2005. *In vitro* effects of water-soluble metals present in UK particulate matter. *Exp Lung Res* 31:671–83.
- Metzger KB, Tolbert PE, Klein M, Peel JL, Flanders WD, Todd K, Mulholland JA, Ryan PB, and Frumkin H. 2004. Ambient air pollution and cardiovascular emergency department visits. *Epidemiology* 15:46–56.
- Michaud JP, Grove JS, and Krupitsky D. 2004. Emergency department visits and "vog"-related air quality in Hilo, Hawai'i. *Environ Res* 95:11–19.
- Migliaretti G and Cavallo F. 2004. Urban air pollution and asthma in children. *Pediatr Pulmonol* 38:198–203.
- Miller FJ. 2000. Dosimetry of particles: critical factors having risk assessment implications. *Inhal Toxicol* 12:389–95.
- Miller FJ, Anjilvel S, Menache, MG, Asgharian B and Gerrity TR. 1995. Dosimetric issues relating to particulate toxicity. *Inhal Toxicol* 7:615–32.
- Miller RL, Garfinkel R, Horton M, Camann D, Perera FP, Whyatt RM, and Kinney PL. 2004. Polycyclic aromatic hydrocarbons, environmental tobacco smoke, and respiratory symptoms in an inner-city birth cohort. *Chest* 126:1071–8.
- Mills NL, Amin N, Robinson SD, Anand A, Davies J, Patel D, De la Fuente JM, Cassee FR, Boon NA, Macnee W, Millar AM, Donaldson K, and Newby DE. 2006. Do inhaled carbon nanoparticles translocate directly into the circulation in humans? *Am J Respir Crit Care Med* 173:426–31.
- Millstein J, Gilliland F, Berhane K, Gauderman WJ, McConnell R, and Avol E. 2004. Effects of ambient air pollutants on asthma medication use and wheezing among fourth-grade school children from 12 Southern California communities enrolled in The Children's Health Study. *Arch Environ Health* 59:505–14.
- Minard KR, Einstein DR, Jacob RE, Kabilan S, Kuprat AP, Timchalk CA, Trease LL, and Corley RA. 2006. Application of magnetic resonance (MR) imaging for the development and validation of computational fluid dynamic (CFD) models of the rat respiratory system. *Inhal Toxicol* 18:787–94.
- Möller W, Hofer T, Ziesenis A, Karg E, and Heyder J. 2002. Ultrafine particles cause cytoskeletal dysfunctions in macrophages. *Toxicol Appl Pharmacol* 182:197–207.
- Möller W, Haussinger K, Winkler-Heil R, Stahlhofen W, Meyer T, Hofmann W, and Heyder J. 2004. Mucociliary and long-term particle clearance in the airways of healthy nonsmoker subjects. *J Appl Physiol* 97:2200–06.
- Molnar P, Gustafson P, Johannesson S, Boman J, Barregard L, and Sallsten G. 2005. Domestic wood burning and PM_{2.5} trace elements: personal exposures, indoor and outdoor levels. *Atmos Env* 39:2643–53.
- Molnar P, Johannesson S, Boman J, Barregard L, and Gallsten G. 2006. Personal exposures and indoor, residential outdoor, and urban background levels of fine particle trace elements in the general population. *J Environ Monitor* 8:543–51.
- Monn C, Fendt R, and Koller T. 2002. Ambient PM(10) extracts inhibit phagocytosis of defined inert model particles by alveolar macrophages. *Inhal Toxicol* 14:369–85.

- Montoya LD, Lawrence J, Murthy GGK, Sarnat JA, Godleski JJ, and Koutrakis P. 2004. Continuous measurements of ambient particle deposition in human subjects. *Aerosol Sci Tech* 38:980–90.
- Moolgavkar SH. 2003. Air pollution and daily mortality in two U.S. counties: season-specific analyses and exposure-response relationships. *Inhal Toxicol* 15:877–907.
- Moore D, Copes R, Fisk R, Joy R, Chan K, and Brauer M. 2006. Population health effects of air quality changes due to forest fires In British Columbia in 2003. *Can J Publ Health* 97:105-108.
- Morawska L, He CR, Hitchins J, Gilbert D, and Parappukkaran S. 2001. The relationship between indoor and outdoor airborne particles in the residential environment. *Atmos Env* 35:3463–73.
- Morishita M, Keeler G, Wagner J, Marsik F, Timm E, Dvonch J, and Harkema J. 2004. Pulmonary retention of particulate matter is associated with airway inflammation in allergic rats exposed to air pollution in urban Detroit. *Inhal Toxicol* 16:663–74.
- Moshhammer H and Neuberger M. 2003. The active surface of suspended particles as a predictor of lung function and pulmonary symptoms in Austrian school children. *Atmos Environ* 37:1737–44.
- Moshhammer H, Hutter HP, Hauck H, and Neuberger M. 2006. Low levels of air pollution induce changes of lung function in a panel of schoolchildren. *Eur Respir J* 27:1138–43.
- Moskal A, Makowski L, Sosnowski TR, and Gradon L. 2006. Deposition of fractal-like aerosol aggregates in a model of human nasal cavity. *Inhal Toxicol* 18:725–31.
- Mosley RB, Greenwell DJ, Sparks LE, Guo Z, Tucker WG, Fortmann R, and Whitfield C. 2001. Penetration of ambient fine particles into the indoor environment. *Aerosol Sci Tech* 34:127–36.
- Mosqueron L, Momas I, and Le Moullec Y. 2002. Personal exposure of Paris office workers to nitrogen dioxide and fine particles. *Occup Environ Med* 59:550–5.
- Moss OR and Wong VA. 2006. When nanoparticles get in the way: impact of projected area on *in vivo* and *in vitro* macrophage function. *Inhal Toxicol* 18:711–16.
- Moyer CF, Kodavanti UP, Haseman JK, Costa DL, and Nyska A. 2002. Systemic vascular disease in male B6C3F1 mice exposed to particulate matter by inhalation: studies conducted by the National Toxicology Program. *Toxicol Pathol* 30:427–34.
- Muggenburg BA, Benson JM, Barr EB, Kubatko J, and Tilley LP. 2003. Short-term inhalation of particulate transition metals has little effect on the electrocardiograms of dogs having preexisting cardiac abnormalities. *Inhal Toxicol* 15:357–71.
- Murakami Y and Ono M. 2006. Myocardial infarction deaths after high level exposure to particulate matter. *J Epidemiol Commun Health* 60:262–6.
- Mussali-Galante P, Rodriguez-Lara V, Hernandez-Tellez B, Avila-Costa MR, Colin-Barenque L, Bizarro-Nevarez P, Martinez-Levy G, Rojas-Lemus M, Pinon-Zarate G, Saldivar-Osorio L, Diaz-Beck P, Herrera-Enriquez MA, Tovar-Sanchez E, and Fortoul TI. 2005. Inhaled vanadium pentoxide decrease gamma-tubulin of mouse testes at different exposure times. *Toxicol Ind Health* 21:215–22.
- Mutlu GM, Snyder C, Bellmeyer A, Wang H, Hawkins K, Soberanes S, Welch LC, Ghio AJ, Chandel NS, Kamp D, Sznajder JI, and Budinger GR. 2006. Airborne particulate matter inhibits alveolar fluid reabsorption in mice via oxidant generation. *Am J Respir Cell Mol Biol* 34:670–6.

- Na K and Cocker III DR. 2005. Organic and elemental carbon concentrations in fine particulate matter in residences, schoolrooms, and outdoor air in Mira Loma, California. *Atmos Env* 39:3325–33.
- Nadziejko C, Fang K, Nadziejko E, Narciso SP, Zhong M, and Chen LC. 2002. Immediate effects of particulate air pollutants on heart rate and respiratory rate in hypertensive rats. *Cardiovasc Toxicol* 2:245–52.
- Nadziejko C, Fang K, Narciso S, Zhong M, Su WC, Gordon T, Nadas A, and Chen LC. 2004. Effect of particulate and gaseous pollutants on spontaneous arrhythmias in aged rats. *Inhal Toxicol* 16:373–80.
- Nam HY, Choi BH, Lee JY, Lee SG, Kim YH, Lee KH, Yoon HK, Song JS, Kim HJ, and Lim Y. 2004. The role of nitric oxide in the particulate matter (PM_{2.5})-induced NFκB activation in lung epithelial cells. *Toxicol Lett* 148:95–102.
- Navrotsky A. 2001. Thermochemistry of nanomaterials. *Reviews in Mineralogy and Geochemistry* 44:73–103.
- Nazaroff WW, Gadgil AJ, and Weschler CJ. 1993. Critique of the use of deposition velocity in modeling indoor air quality. West Conshohocken, PA: ASTM Special Technical Publication 81-104.
- Nazaroff WW. 2004. Indoor particle dynamics. *Indoor Air* 14:175–83.
- Neas L, Stolzel M, Paatero P, Hopke PK, and Thurston GD. 2006. PM source apportionment and health effects. 3. Investigation of inter-method variations in associations between estimated source contributions of PM_{2.5} and daily mortality in Phoenix, AZ. *J Expo Sci Environ Epidemiol* 16:311–20.
- Nemmar A, Hoylaerts MF, Hoet PH, Vermeylen J, and Nemery B. 2003. Size effect of intratracheally instilled particles on pulmonary inflammation and vascular thrombosis. *Toxicol Appl Pharmacol* 186:38–45.
- Nemmar A, Nemery B, Hoet PH, Van Rooijen N, and Hoylaerts MF. 2005. Silica particles enhance peripheral thrombosis: key role of lung macrophage-neutrophil cross-talk. *Am J Respir Crit Care Med* 171:872–9.
- Nerriere E, Zmirou-Navier D, Blanchard O, Momas I, Ladner J, Le Moullec Y, Personnaz MB, Lameloise P, Delmas W, Target A, and Desqueyroux H. 2005. Can we use fixed ambient air monitors to estimate population long-term exposure to air pollutants? The case of spatial variability in the Genotox ER study. *Environ Res* 97:32-42.
- Neuberger M, Schimek MG, Horak Jr F, Moshhammer H, Kundi M, Frischer T, Gomiscek B, Puxbaum H, and Hauck H. 2004. Acute effects of particulate matter on respiratory diseases, symptoms and functions: epidemiological results of the Austrian Project on Health Effects of Particulate Matter (AUPHEP). *Atmos Environ* 38:3971–81.
- Newhouse CP and Levetin E. 2004. Correlation of environmental factors with asthma and rhinitis symptoms in Tulsa, OK. *Ann Allergy Asthma Immunol* 92:356–66.
- Newman SP, Pitcairn GR, and Dalby RN. 2004. Drug delivery to the nasal cavity: *in vitro* and *in vivo* assessment. *Crit Rev Ther Drug Carrier Syst* 21:21–66.
- Nikasinovic L, Just J, Sahraoui F, Seta N, Grimfeld A, and Momas I. 2006. Nasal inflammation and personal exposure to fine particles PM_{2.5} in asthmatic children. *J Allergy Clin Immunol* 117:1382–8.

- Noullett M, Jackson PL, and Brauer M. 2006. Winter measurements of children's personal exposure and ambient fine particle mass, sulphate and light absorbing components in a northern community. *Atmos Env* 40:1971–90.
- Nurkiewicz TR, Porter DW, Barger M, Castranova V, and Boegehold MA. 2004. Particulate matter exposure impairs systemic microvascular endothelium-dependent dilation. *Environ Health Perspect* 112:1299–1306.
- Nurkiewicz TR, Porter DW, Barger M, Millecchia L, Rao KM, Marvar PJ, Hubbs AF, Castranova V, and Boegehold MA. 2006. Systemic microvascular dysfunction and inflammation after pulmonary particulate matter exposure. *Environ Health Perspect* 114:412–19.
- Oberdörster G, Sharp Z, Atudorei V, Elder A, Gelein R, Kreyling W, and Cox C. 2004. Translocation of inhaled ultrafine particles to the brain. *Inhal Toxicol* 16:437–45.
- Oberdörster G, Oberdörster E, and Oberdörster J. 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. *Environ Health Perspect* 113:823–39.
- Obot CJ, Morandi MT, Beebe TP, Hamilton RF, and Holian A. 2002. Surface components of airborne particulate matter induce macrophage apoptosis through scavenger receptors. *Toxicol Appl Pharmacol* 184:98–106.
- Oftedal B, Nafstad P, Magnus P, Bjorkly S, and Skrondal A. 2003. Traffic related air pollution and acute hospital admission for respiratory diseases in Drammen, Norway 1995–2000. *Eur J Epidemiol* 18:671–5.
- Oglesby L, Künzli N, Rössli M, Braun-Fahrländer C, Mathys P, Stern W, Jantunen M, and Koussa A. 2000. Validity of ambient levels of fine particles as surrogate for personal exposure to outdoor air pollution—results of the European EXPOLIS-EAS study (Swiss Center Basel). *J Air Waste Man Assoc* 50:1251–61.
- Ohura T, Amagai T, Fusaya M, and Matsushita H. 2004. Polycyclic aromatic hydrocarbons in indoor and outdoor environments and factors affecting their concentrations. *Environ Sci Technol* 38:77–83.
- Ohura T, Noda T, Amagai T, and Fusaya M. 2005. Prediction of personal exposure to PM_{2.5} and carcinogenic polycyclic aromatic hydrocarbons by their concentrations in residential microenvironments. *Environ Sci Technol* 39:5592–9.
- Oldham MJ. 2006. Challenges in validating CFD-derived inhaled aerosol deposition predictions. *Inhal Toxicol* 18:781–6.
- Oldham MJ and Robinson RJ. 2006. Calculated deposition in growing tracheobronchial airways: effect of growth-rate assumptions. *Inhal Toxicol* 18:803–8.
- Omori T, Fujimoto G, Yoshimura I, Nitta H, and Ono M. 2003. Effects of particulate matter on daily mortality in 13 Japanese cities. *J Epidemiol* 13:314–22.
- O'Neill MS, Loomis D, Borja Aburto VH, Gold D, Hertz-Picciotto I, and Castillejos M. 2004. Do associations between airborne particles and daily mortality in Mexico City differ by measurement method, region, or modeling strategy? *J Expo Anal Environ Epidemiol* 14:429–39.
- O'Neill MS, Veves A, Zanobetti A, Sarnat JA, Gold DR, Economides PA, Horton ES, and Schwartz J. 2005. Diabetes enhances vulnerability to particulate air pollution-associated impairment in vascular reactivity and endothelial function. *Circulation* 111:2913–20.
- Osornio-Vargas AR, Bonner JC, Alfaro-Moreno E, Martinez L, Garcia-Cuellar C, Ponce-de-Leon Rosales S, Miranda J, and Rosas I. 2003. Proinflammatory and cytotoxic effects of Mexico City

- air pollution particulate matter *in vitro* are dependent on particle size and composition. *Environ Health Perspect* 111:1289–93.
- Ostro B, Broadwin R, Green S, Feng WY, and Lipsett M. 2006. Fine particulate air pollution and mortality in nine California counties: results from CALFINE. *Environ Health Perspect* 114:29–33.
- Ott W, Wallace L, and Mage D. 2000. Predicting particulate (PM₁₀) personal exposure distributions using a random component superposition statistical model. *J Air Waste Man Assoc* 50:1390–1406.
- Özkaynak H, Zue J, Weker R, Butler D, Koutrakis P, and Spengler J. 1996a. The Particle Team (PTEAM) Study: analysis of the data final report Vol III. Washington, DC: U.S. Environmental Protection Agency. Publication No. EPA 600/R-95/098.
- Özkaynak H, Xue J, Spengler J, Wallace L, Pellizzari E, and Jenkins P. 1996b. Personal exposure to airborne particles and metals: results from the Particle TEAM study in Riverside, California. *J Expo Analysis Environ Epidemiol* 6:57–78.
- Pagan I, Costa DL, McGee JK, Richards JH, and Dye JA. 2003. Metals mimic airway epithelial injury induced by *in vitro* exposure to Utah Valley ambient particulate matter extracts. *J Toxicol Environ Health A* 66:1087–1112.
- Park H, Lee B, Ha EH, Lee JT, Kim H, and Hong YC. 2002. Association of air pollution with school absenteeism due to illness. *Arch Pediatr Adolesc Med* 156:1235–9.
- Park JH, Han KT, Eu KJ, Kim JS, Chung KH, Park B, Yang GS, Lee KH, and Cho MH. 2005. Diffusion flame-derived fine particulate matters doped with iron caused genotoxicity in B6C3F1 mice. *Toxicol Ind Health* 21:57–65.
- Park JW, Lim YH, Kyung SY, An CH, Lee SP, Jeong SH, and Ju YS. 2005. Effects of ambient particulate matter on peak expiratory flow rates and respiratory symptoms of asthmatics during Asian dust periods in Korea. *Respirology* 10:470–6.
- Park SK, O'Neill MS, Vokonas PS, Sparrow D, and Schwartz J. 2005. Effects of air pollution on heart rate variability: the VA normative aging study. *Environ Health Perspect* 113:304–9.
- Park SK, O'Neill MS, Wright RO, Hu H, Vokonas PS, Sparrow D, Suh H, and Schwartz J. 2006. HFE genotype, particulate air pollution, and heart rate variability: a gene–environment interaction. *Circulation* 114:2798–805.
- Parker JD, Woodruff TJ, Basu R, and Schoendorf KC. 2005. Air pollution and birth weight among term infants in California. *Pediatrics* 115:121–8.
- Partridge GP and Javeed NM. Atmospheric aerosols and the human respiratory system: health effects and model development. Air and Waste Management Association 2004. *In Proceedings of the 97th Annual A&WMA Conference & Exhibition: June 22–25, 2003, Indianapolis, IA, 3201–12.*
- Partti-Pellinen K, Marttila O, Ahonen A, Suominen O, and Haahtela T. 2000. Penetration of nitrogen oxides and particles from outdoor into indoor air and removal of the pollutants through filtration of incoming air. *Indoor Air* 10:126–32.
- Paschold H, Li WW, Morales H, and Walton J. 2003. Laboratory study of the impact of evaporative coolers on indoor PM concentrations. *Atmos Env* 37:1075–86.
- Patterson E and Eatough DJ. 2000. Indoor/outdoor relationships for ambient PM_{2.5} and associated pollutants: epidemiological implications in Lindon, Utah. *J Air Waste Man Assoc* 50:103–10.

- Peacock JL, Symonds P, Jackson P, Bremner SA, Scarlett JF, Strachan DP, and Anderson HR. 2003. Acute effects of winter air pollution on respiratory function in schoolchildren in southern England. *Occup Environ Med* 60:82–9.
- Pedersen DU, Durant JL, Penman BW, Crespi CL, Hemond HF, Lafleur AL, and Cass GR. 2004. Human-cell mutagens in respirable airborne particles in the northeastern United States. 1. Mutagenicity of fractionated samples. *Environ Sci Technol* 38:682–9.
- Pedersen DU, Durant JL, Taghizadeh K, Hemond HF, Lafleur AL, and Cass GR. 2005. Human cell mutagens in respirable airborne particles from the northeastern United States. 2. Quantification of mutagens and other organic compounds. *Environ Sci Technol* 39:9547–60.
- Peel JL, Tolbert PE, Klein M, Metzger KB, Flanders WD, Todd K, Mulholland JA, Ryan PB, and Frumkin H. 2005. Ambient air pollution and respiratory emergency department visits. *Epidemiology* 16:164–74.
- Pekkanen J, Peters A, Hoek G, Tiittanen P, Brunekreef B, de Hartog J, Heinrich J, Ibaldo-Mulli A, Kreyling WG, Lanki T, Timonen KL, and Vanninen E. 2002. Particulate air pollution and risk of ST-segment depression during repeated submaximal exercise tests among subjects with coronary heart disease: the Exposure and Risk Assessment for Fine and Ultrafine Particles in Ambient Air (ULTRA) study. *Circulation* 106:933–8.
- Peled R, Friger M, Bolotin A, Bibi H, Epstein L, Pilpel D, and Scharf S. 2005. Fine particles and meteorological conditions are associated with lung function in children with asthma living near two power plants. *Public Health* 119:418–25.
- Pellizzari ED, Mason RE, Clayton CA, Thomas KW, Cooper S, Piper L, Rodes C, Goldberg M, Roberds J, and Michael L. 1998. Final Report - Manganese exposure study (Toronto). Research Triangle Park, NC: Analytical and Chemical Sciences, Research Triangle Institute. (RTI/6312/02-01 F).
- Pellizzari ED, Clayton CA, Rodes CE, Mason RE, Piper LL, Fort B, Pfeifer G, and Lynam D. 1999. Particulate matter and manganese exposures in Toronto, Canada. *Atmos Env* 33:721–34.
- Pellizzari ED, Clayton CA, Rodes CE, Mason RE, Piper LL, Fort B, Pfeifer G, and Lynam D. 2001. Particulate matter and manganese exposures in Indianapolis, Indiana. *J Expo Analysis Environ Epidemiol* 11:423–40.
- Peluso M, Munnia A, Hoek G, Krzyzanowski M, Veglia F, Airoidi L, Autrup H, Dunning A, Garte S, Hainaut P, Malaveille C, Gormally E, Matullo G, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Trichopoulos D, Kaladidi A, Palli D, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Kumle M, Gonzalez CA, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Berglund G, Janzon L, Jarvholm B, Day NE, Key TJ, Saracci R, Kaaks R, Riboli E, and Vineis P. 2005. DNA adducts and lung cancer risk: a prospective study. *Cancer Res* 65:8042–8.
- Penard-Morand C, Charpin D, Raheison C, Kopferschmitt C, Caillaud D, and Lavaud F. 2005. Long-term exposure to background air pollution related to respiratory and allergic health in schoolchildren. *Clin Exp Allergy* 35:1279–87.
- Peng RD, Dominici F, Pastor-Barriuso R, Zeger SL, and Samet JM. 2005. Seasonal analyses of air pollution and mortality in 100 US cities. *Am J Epidemiol* 161:585–94.
- Penttinen P, Tiittanen P, and Pekkanen J. 2004. Mortality and air pollution in metropolitan Helsinki, 1988–1996. *Scand J Work Environ Health* 30 Suppl 2:19–27.
- Penttinen P, Vallius M, Tiittanen P, Ruuskanen J, and Pekkanen J. 2006. Source-specific fine particles in urban air and respiratory function among adult asthmatics. *Inhal Tox* 18:191–8.

- Perera FP, Rauh V, Whyatt RM, Tsai WY, Tang D, Diaz D, Hoepner L, Barr D, Tu YH, Camann D, and Kinney P. 2006. Effect of prenatal exposure to airborne polycyclic aromatic hydrocarbons on neurodevelopment in the first 3 years of life among inner-city children. *Environ Health Perspect* 114:1287–92.
- Pfeifer GD, Harrison RM, and Lynam DR. 1999. Personal exposures to airborne metals in London taxi drivers and office workers in 1995 and 1996. *Sci Total Env* 235:253–60.
- Phalen RF and Oldham MJ. 2006. Aerosol dosimetry considerations. *Clin Occup Environ Med* 5:773–84.
- Pierse N, Rushton L, Harris R, Kuehni C, Silverman M, Grigg J. 2006. Locally-generated particulate pollution and respiratory symptoms in young children. *Thorax* 61:216–20.
- Pietropaoli AP, Frampton MW, Hyde RW, Morrow PE, Oberdörster G, Cox C, Speers DM, Frasier LM, Chalupa DC, Huang LS, and Utell MJ. 2004. Pulmonary function, diffusing capacity, and inflammation in healthy and asthmatic subjects exposed to ultrafine particles. *Inhal Toxicol* 16 Suppl 1:59–72.
- Pilger A and Rüdiger HW. 2006. 8-Hydroxy-2'-deoxyguanosine as a marker of oxidative DNA damage related to occupational and environmental exposures. *Int Arch Occup Environ Health* 80:1–15.
- Pinkerton KE, Zhou YM, Teague SV, Peake JL, Walther RC, Kennedy IM, Leppert VJ, and Aust AE. 2004. Reduced lung cell proliferation following short-term exposure to ultrafine soot and iron particles in neonatal rats: key to impaired lung growth? *Inhal Toxicol* 16 Suppl 1:73–81.
- Pino P, Walter T, Oyarzun M, Villegas R, and Romieu I. 2004. Fine particulate matter and wheezing illnesses in the first year of life. *Epidemiology* 15:702–8.
- Pitard A, Zeghnoun A, Courseaux A, Lambert J, Delmas V, Fossard JL, and Villet H. 2004. Short-term associations between air pollution and respiratory drug sales. *Environ Res* 95:43–52.
- Pohjola SK, Lappi M, Honkanen M, Rantanen L, and Savela K. 2003a. DNA binding of polycyclic aromatic hydrocarbons in a human bronchial epithelial cell line treated with diesel and gasoline particulate extracts and benzo[a]pyrene. *Mutagenesis* 18:429–38.
- Pohjola SK, Lappi M, Honkanen M, and Savela K. 2003b. Comparison of mutagenicity and calf thymus DNA adducts formed by the particulate and semivolatile fractions of vehicle exhausts. *Environ Mol Mutagen* 42:26–36.
- Poma A, Limongi T, Pisani C, Granato V, and Picozzi P. 2006. Genotoxicity induced by fine urban air particulate matter in the macrophages cell line RAW 264.7. *Toxicol In Vitro* 20:1023–9.
- Pope CA. 1989. Respiratory disease associated with community air pollution and a steel mill, Utah Valley. *Am J Public Health* 79:623–8.
- Pope CA 3rd, Thun MJ, Namboodiri MM, Dockery DW, Evans JS, Speizer FE, and Heath CW Jr. 1995. Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. *Am J Respir Crit Care Med* 151:669–74.
- Pope C A 3rd. 2000. Invited Commentary: Particulate matter-mortality exposure-response relations and threshold. *Am J Epidemiol.* 152:407–12.
- Pope CA 3rd, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, and Thurston GD. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 287:1132–41.

Pope CA 3rd, Hansen ML, Long RW, Nielsen KR, Eatough NL, Wilson WE, and Eatough DJ. 2004a. Ambient particulate air pollution, heart rate variability, and blood markers of inflammation in a panel of elderly subjects. *Environ Health Perspect* 112:339–45.

Pope CA 3rd, Burnett RT, Thurston GD, Thun MJ, Calle EE, Krewski D, and Godleski JJ. 2004b. Cardiovascular mortality and long-term exposure to particulate air pollution: epidemiological evidence of general pathophysiological pathways of disease. *Circulation* 109:71–7.

Poster DL, Schantz MM, Sander LC, and Wise SA. 2006. Analysis of polycyclic aromatic hydrocarbons (PAHs) in environmental samples: a critical review of gas chromatographic (GC) methods. *Anal Bioanal Chem* 386:859–81.

Pott F and Roller M. 2005. Carcinogenicity study with nineteen granular dusts in rats. *Euro J Oncol* 10:249–81.

Pozzi R, De Berardis B, Paoletti L, and Guastadisegni C. 2003. Inflammatory mediators induced by coarse (PM_{2.5-10}) and fine (PM_{2.5}) urban air particles in RAW 264.7 cells. *Toxicology* 183:243–54.

Pozzi R, De Berardis B, Paoletti L, and Guastadisegni C. 2005. Winter urban air particles from Rome (Italy): effects on the monocytic-macrophagic RAW 264.7 cell line. *Environ Res* 99:344–54.

Pradhan A, Waseem M, Dogra S, Khanna AK, and Kaw JL. 2005. Alterations in bronchoalveolar lavage constituents, oxidant/antioxidant status, and lung histology following intratracheal instillation of respirable suspended particulate matter. *J Environ Pathol Toxicol Oncol* 24:19–32.

Preutthipan A, Udomsubpayakul U, Chaisupamongkollarp T, and Pentamwa P. 2004. Effect of PM₁₀ pollution in Bangkok on children with and without asthma. *Pediatr Pulmonol* 37:187–92.

Prieditis H and Adamson IY. 2002. Comparative pulmonary toxicity of various soluble metals found in urban particulate dusts. *Exp Lung Res* 28:563–76.

Proctor SD, Dreher KL, Kelly SE, and Russell JC. 2006. Hypersensitivity of prediabetic JCR:LA-cp rats to fine airborne combustion particle-induced direct and noradrenergic-mediated vascular contraction. *Toxicol Sci* 90:385–91.

Prows DR, McDowell SA, Aronow BJ, and Leikauf GD. 2003. Genetic susceptibility to nickel-induced acute lung injury. *Chemosphere* 51:1139–48.

Quintana PJ, Valenzia JR, Delfino RJ, and Liu LJ. 2001. Monitoring of 1-min personal particulate matter exposures in relation to voice-recorded time-activity data. *Environ Res* 87:199–213.

Rabinovitch N, Zhang L, Murphy JR, Vedal S, Dutton SJ, and Gelfand EW. 2004. Effects of wintertime ambient air pollutants on asthma exacerbations in urban minority children with moderate to severe disease. *J Allergy Clin Immunol* 114:1131–7.

Rabinovitch N, Strand M, and Gelfand EW. 2006. Particulate levels are associated with early asthma worsening in children with persistent disease. *Am J Respir Crit Care Med* 173:1098–1105.

Rahman Q, Lohani M, Dopp E, Pemsel H, Jonas L, Weiss DG, and Schiffmann D. 2002. Evidence that ultrafine titanium dioxide induces micronuclei and apoptosis in Syrian hamster embryo fibroblasts. *Environ Health Perspect* 110:797–800.

- Ramadour M, Burel C, Lanteaume A, Vervloet D, Charpin D, Brisse F, Dutau H, and Charpin D. 2000. Prevalence of asthma and rhinitis in relation to long-term exposure to gaseous pollutants. *Allergy* 55:1163–9.
- Ramage L and Guy K. 2004. Expression of C-reactive protein and heat-shock protein-70 in the lung epithelial cell line A549, in response to PM₁₀ exposure. *Inhal Toxicol* 16:447–52.
- Ransom M and Pope CA. 1992. Elementary school absences and PM₁₀ pollution in Utah Valley. *Environ Res* 58:204–19.
- Ranzi A, Gambini M, Spattini A, Galassi C, Sesti D, Bedeschi M, Messori A, Baroni A, Cavagni G, and Lauriola P. 2004. Air pollution and respiratory status in asthmatic children: hints for a locally based preventive strategy. AIRE study. *Eur J Epidemiol* 19:567–76.
- Raunemaa T, Kulmala M, Saari H, Olin M, and Kulmala MH. 1989. Indoor air aerosol model: transport indoors and deposition of fine and coarse particles. *Aerosol Sci Tech* 11:11–25.
- Reff A, Turpin BJ, Porcja RJ, Giovenetti R, Cui W, Weisel CP, Zhang J, Kwon J, Alimokhtari S, Morandi M, Stock T, Maberti S, Colome S, Winer A, Shendell D, Jones J, and Farrar C. 2005. Functional group characterization of indoor, outdoor, and personal PM: results from RIOPA. *Indoor Air* 15:53–61.
- Reibman J, Hsu Y, Chen LC, Kumar A, Su WC, Choy W, Talbot A, and Gordon T. 2002. Size fractions of ambient particulate matter induce granulocyte macrophage colony-stimulating factor in human bronchial epithelial cells by mitogen-activated protein kinase pathways. *Am J Respir Cell Mol Biol* 27:455–62.
- Renwick LC, Brown D, Clouter A, and Donaldson K. 2004. Increased inflammation and altered macrophage chemotactic responses caused by two ultrafine particle types. *Occup Environ Med* 61:442–7.
- Reponen T, Grinshpun SA, Trakumas S, Martuzevicius D, Wang ZM, LeMasters G, Lockey JE, and Biswas P. 2003. Concentration gradient patterns of aerosol particles near interstate highways in the Greater Cincinnati airshed. *J Environ Monitor* 5:557–62.
- Ress NB, Chou BJ, Renne RA, Dill JA, Miller RA, Roycroft JH, Hailey JR, Haseman JK, and Bucher JR. 2003. Carcinogenicity of inhaled vanadium pentoxide in F344/N rats and B6C3F1 mice. *Toxicol Sci* 74:287–96.
- Rhoden CR, Lawrence J, Godleski JJ, and Gonzalez-Flecha B. 2004. N-acetylcysteine prevents lung inflammation after short-term inhalation exposure to concentrated ambient particles. *Toxicol Sci* 79:296–303.
- Rhoden CR, Wellenius GA, Ghelfi E, Lawrence J, and Gonzalez-Flecha B. 2005. PM-induced cardiac oxidative stress and dysfunction are mediated by autonomic stimulation. *Biochim Biophys Acta* 1725:305–13.
- Rich DQ, Schwartz J, Mittleman MA, Link M, Luttmann-Gibson H, Catalano PJ, Speizer FE, and Dockery DW. 2005. Association of short-term ambient air pollution concentrations and ventricular arrhythmias. *Am J Epidemiol* 161:1123–32.
- Rich DQ, Mittleman MA, Link MS, Schwartz J, Luttmann-Gibson H, Catalano PJ, Speizer FE, Gold DR, and Dockery DW. 2006a. Increased risk of paroxysmal atrial fibrillation episodes associated with acute increases in ambient air pollution. *Environ Health Perspect* 114:120–3.
- Rich DQ, Kim MH, Turner JR, Mittleman MA, Schwartz J, Catalano PJ, and Dockery DW. 2006b. Association of ventricular arrhythmias detected by implantable cardioverter defibrillator and ambient air pollutants in Saint Louis, Missouri. *Occup Environ Med* 63, 591–6.

- Rich KE, Petkau J, Vedal S, and Brauer M. 2004. A case-crossover analysis of particulate air pollution and cardiac arrhythmia in patients with implantable cardioverter defibrillators. *Inhal Toxicol* 16:363–72.
- Riechelmann H, Rettinger G, Weschta M, Keck T, and Deutsche T. 2003. Effects of low-toxicity particulate matter on human nasal function. *J Occup Environ Med* 45:54–60.
- Riechelmann H, Rettinger G, Lautebach S, Schmittinger S, and Deutsche T. 2004. Short-term exposure to urban dust alters the mediator release of human nasal mucosa. *J Occup Environ Med* 46:316–22.
- Riediker M, Williams R, Devlin R, Griggs T, and Bromberg P. 2003. Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. *Environ Sci Technol* 37:2084–93.
- Riediker M, Cascio WE, Griggs TR, Herbst MC, Bromberg PA, Neas L, Williams RW, and Devlin RB. 2004a. Particulate matter exposure in cars is associated with cardiovascular effects in healthy young men. *Am J Respir Crit Care Med* 169:934–40.
- Riediker M, Devlin RB, Griggs TR, Herbst MC, Bromberg PA, Williams RW, and Cascio WE. 2004b. Cardiovascular effects in patrol officers are associated with fine particulate matter from brake wear and engine emissions. *Part Fibre Toxicol* 1:2.
- Riley MR, Boesewetter DE, Kim AM, and Sirvent FP. 2003. Effects of metals Cu, Fe, Ni, V, and Zn on rat lung epithelial cells. *Toxicology* 190:171–84.
- Riley WJ, McKone TE, Lai AC, and Nazaroff WW. 2002. Indoor particulate matter of outdoor origin: importance of size-dependent removal mechanisms. *Environ Sci Technol* 36:200–7.
- Riojas-Rodriguez H, Escamilla-Cejudo JA, Gonzalez-Hermosillo JA, Tellez-Rojo MM, Vallejo M, Santos-Burgoa C, and Rojas-Bracho L. 2006. Personal PM_{2.5} and CO exposures and heart rate variability in subjects with known ischemic heart disease in Mexico City. *J Expo Sci Environ Epidemiol* 16:131–7.
- Ritz B and Yu F. 1999. The effect of ambient carbon monoxide on low birth weight among children born in southern California between 1989 and 1993. *Environ Health Perspect* 107:17–25.
- Ritz B, Yu F, Chapa G, and Fruin S. 2000. Effect of air pollution on preterm birth among children born in Southern California between 1989 and 1993. *Epidemiology* 11:502–11.
- Ritz B, Yu F, Fruin S, Chapa G, Shaw GM, and Harris JA. 2002. Ambient air pollution and risk of birth defects in Southern California. *Am J Epidemiol* 155:17–25.
- Ritz B, Wilhelm M, and Zhao Y. 2006. Air pollution and infant death in southern California, 1989–2000. *Pediatrics* 118:493–502.
- Rivero DH, Sasaki C, Lorenzi-Filho G, and Saldiva PH. 2005a. PM_{2.5} induces acute electrocardiographic alterations in healthy rats. *Environ Res* 99:262–6.
- Rivero DH, Soares SR, Lorenzi-Filho G, Saiki M, Godleski JJ, Antonangelo L, Dolhnikoff M, and Saldiva PH. 2005b. Acute cardiopulmonary alterations induced by fine particulate matter of Sao Paulo, Brazil. *Toxicol Sci* 85:898–905.
- Roberts ES, Richards JH, Jaskot R, and Dreher KL. 2003. Oxidative stress mediates air pollution particle-induced acute lung injury and molecular pathology. *Inhal Toxicol* 15:1327–46.

- Roberts E, Charboneau L, Espina V, Liotta L, Petricoin E, and Dreher K. 2004a. Application of laser capture microdissection and protein microarray technologies in the molecular analysis of airway injury following pollution particle exposure. *J Toxicol Environ Health A* 67:851–61.
- Roberts JR, Taylor MD, Castranova V, Clarke RW, and Antonini JM. 2004b. Soluble metals associated with residual oil fly ash increase morbidity and lung injury after bacterial infection in rats. *J Toxicol Environ Health A* 67:251–63.
- Roberts S and Martin MA. 2006. Applying a moving total mortality count to the cities in the NMMAPS database to estimate the mortality effects of particulate matter air pollution. *Occup Environ Med* 63:193–7.
- Rogers JF and Dunlop AL. 2006. Air pollution and very low birth weight infants: A target population? *Pediatrics* 118:156–64.
- Rojas-Bracho L, Suh HH, and Koutrakis P. 2000. Relationships among personal, indoor, and outdoor fine and coarse particle concentrations for individuals with COPD. *J Expo Analysis Environ Epidemiol* 10:294–306.
- Rojas-Bracho L, Suh HH, Oyola P, and Koutrakis P. 2002. Measurements of children's exposures to particles and nitrogen dioxide in Santiago, Chile. *Sci Total Env* 287:249–64.
- Rojas-Bracho L, Suh HH, Catalano PJ, and Koutrakis P. 2004. Personal exposures to particles and their relationships with personal activities for chronic obstructive pulmonary disease patients living in Boston. *J Air Waste Man Assoc* 54:207–17.
- Romieu I, Sienna-Monge JJ, Ramirez-Aguilar M, Tellez-Rojo MM, Moreno-Macias H, Reyes-Ruiz NI, del Rio-Navarro BE, Ruiz-Navarro MX, Hatch G, Slade R, and Hernandez-Avila M. 2002. Antioxidant supplementation and lung functions among children with asthma exposed to high levels of air pollutants. *Am J Respir Crit Care Med* 166:703–9.
- Romieu I, Tellez-Rojo MM, Lazo M, Manzano-Patino A, Cortez-Lugo M, Julien P, Belanger MC, Hernandez-Avila M, and Holguin F. 2005. Omega-3 fatty acid prevents heart rate variability reductions associated with particulate matter. *Am J Respir Crit Care Med* 172:1534–40.
- Romieu I, Ramirez-Aguilar M, Sienna-Monge JJ, Moreno-Macias H, del Rio-Navarro BE, David G, Marzec J, Hernandez-Avila M, and London S. 2006. GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone. *European Respir J* 28:953–9.
- Rondeau V, Berhane K, and Thomas DC. 2005. A three-level model for binary time-series data: the effects of air pollution on school absences in the Southern California Children's Health Study. *Statist Med* 24:1103–15.
- Rosenlund M, Berglind N, Pershagen G, Hallqvist J, Jonson T, and Bellander T. 2006. Long-term exposure to urban air pollution and myocardial infarction. *Epidemiology* 17:383–90.
- Rousseau D, Boswer D, and Mattock C. 2003. A guide to mechanical equipment for healthy indoor environments. Ottawa, ON: Canada Mortgage and Housing Corp. Publication No. 62015.
- Routledge HC and Ayres JG. 2005. Air pollution and the heart. *Occupational Medicine* 55:439–47.
- Routledge HC, Manney S, Harrison RM, Ayres J, and Townend JN. 2006. The effect of inhaled sulphur dioxide and carbon particles on heart rate variability and markers of inflammation and coagulation in human subjects. *Heart* 92:220–7.
- Rückerl R, Ibaldo-Mulli A, Koenig W, Schneider A, Woelke G, Cyrys J, Heinrich J, Marder V, Frampton M, Wichmann HE, and Peters A. 2006. Air pollution and markers of inflammation and coagulation in patients with coronary heart disease. *Am J Respir Crit Care Med* 173:432–41.

- Saber AT, Bornholdt J, Dybdahl M, Sharma AK, Loft S, Vogel U, and Wallin H. 2005. Tumor necrosis factor is not required for particle-induced genotoxicity and pulmonary inflammation. *Arch Toxicol* 79:177–82.
- Sagiv SK, Mendola P, Loomis D, Herring AH, Neas LM, Savitz DA, and Poole C. 2005. A time-series analysis of air pollution and preterm birth in Pennsylvania, 1997–2001. *Environ Health Perspect* 113:602–6.
- Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, and Gilliland FD. 2005. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. *Environ Health Perspect* 113:1638–44.
- Salnikow K, Li X, and Lippmann M. 2004. Effect of nickel and iron co-exposure on human lung cells. *Toxicol Appl Pharmacol* 196:258–65.
- Salonen RO, Halinen AI, Pennanen AS, Hirvonen MR, Sillanpaa M, Hillamo R, Shi T, Borm P, Sandell E, Koskentalo T, and Aarnio P. 2004. Chemical and *in vitro* toxicologic characterization of wintertime and springtime urban-air particles with an aerodynamic diameter below 10 microm in Helsinki. *Scand J Work Environ Health* 30 Suppl 2:80–90.
- Samet JM, Zeger SL, Dominici F, Curriero F, Coursac I, Dockery DW, Schwartz J, and Zanobetti A. 2000. The national morbidity, mortality, and air pollution study. Part II: morbidity, mortality, and air pollution in the United States. Cambridge, MA: Health Effects Institute. Report No. 094-II.
- Samet JM, Silbajoris R, Huang T, and Jaspers I. 2002. Transcription factor activation following exposure of an intact lung preparation to metallic particulate matter. *Environ Health Perspect* 110:985–90.
- Samoli E, Analitis A, Toulomi G, Schwartz J, Anderson HR, Sunyer J, Bisanti L, Zmirou D, Vonk JM, Pekkanen J, Goodman P, Paldy A, Schindler C, and Katsouyanni K. 2005. Estimating the exposure–response relationships between particulate matter and mortality within the APHEA multicity project. *Environ Health Perspect* 113:88–95.
- Sanchez-Carrillo CI, Ceron-Mireles P, Rojas-Martinez MR, Mendoza-Alvarado L, Olaiz-Fernandez G, and Borja-Aburto VH. 2003. Surveillance of acute health effects of air pollution in Mexico City. *Epidemiology* 14:536–44.
- Santini MT, Rainaldi G, Ferrante A, Romano R, Clemente S, Motta A, De Berardis B, Balduzzi M, Paoletti L, and Indovina PL. 2004. Environmental fine particulate matter (PM_{2.5}) activates the RAW 264.7 macrophage cell line even at very low concentrations as revealed by ¹H NMR. *Chem Res Toxicol* 17:63–74.
- Sarnat JA, Koutrakis P, and Suh HH. 2000. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. *J Air Waste Man Assoc* 50:1184–98.
- Sarnat JA, Long CM, Koutrakis P, Coull BA, Schwartz J, and Suh HH. 2002. Using sulfur as a tracer of outdoor fine particulate matter. *Environ Sci Technol* 36:5305–14.
- Sarnat SE, Coull BA, Schwartz J., Gold DR, and Suh HH. 2006a. Factors affecting the association between ambient concentrations and personal exposures to particles and gases. *Environ Health Perspect* 114:649–54.
- Sarnat SE, Coull BA, Ruiz PA, Koutrakis P, and Suh HH. 2006b. The influences of ambient particle composition and size on particle infiltration in Los Angeles, CA, residences. *J Air Waste Man Assoc* 56:186–96.

- Sarnat SE, Suh HH, Coull BA, Schwartz J, Stone PH, and Gold DR. 2006c. Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio. *Occup Environ Med* 63:700–6.
- Sax SN, Bennett DH, Chillrud SN, Ross J, Kinney PL, and Spengler JD. 2006. A cancer risk assessment of inner-city teenagers living in New York City and Los Angeles. *Environ Health Perspect* 114:1558–66.
- Schauer JJ. 2003. Evaluation of elemental carbon as a marker for diesel particulate matter. *J Expo Analysis Environ Epidemiol* 13:443–53.
- Schaumann F, Borm PJ, Herbrich A, Knoch J, Pitz M, Schins RP, Luettig B, Hohlfeld JM, Heinrich J, and Krug N. 2004. Metal-rich ambient particles (particulate matter 2.5) cause airway inflammation in healthy subjects. *Am J Respir Crit Care Med* 170:898–903.
- Schikowski T, Sugiri D, Ranft U, Gehring U, Heinrich J, and Wichmann EH. 2005. Long-term air pollution exposure and living close to busy roads are associated with COPD in women. *Respir Res* 6:152.
- Schildcrout JS, Sheppard L, Lumley T, Slaughter JC, Koenig JQ, and Shapiro GG. 2006. Ambient air pollution and asthma exacerbations in children: an eight-city analysis. *Am J Epidemiol* 164:505–17.
- Schins RPF, Knaapen MAD, Weishaupt C, Winzer A, and Borm PJA. 2002. Cytotoxic and inflammatory effects of coarse and fine particulate matter in macrophages and epithelial cells. *Ann Occup Hyg* 46 Suppl 1:203–6.
- Schins RP, Lightbody JH, Borm PJ, Shi T, Donaldson K, and Stone V. 2004. Inflammatory effects of coarse and fine particulate matter in relation to chemical and biological constituents. *Toxicol Appl Pharmacol* 195:1–11.
- Schreuder AB, Larson TV, Sheppard L, and Claiborn CS. 2006. Ambient woodsmoke and associated respiratory emergency department visits in Spokane, Washington. *Int J Occup Environ Health* 12:147–53.
- Schwartz J, Litonjua A, Suh H, Verrier M, Zanobetti A, Syring M, Nearing B, Verrier R, Stone P, MacCallum G, Speizer FE, and Gold DR. 2005a. Traffic related pollution and heart rate variability in a panel of elderly subjects. *Thorax* 60:455–61.
- Schwartz J, Park SK, O'Neill MS, Vokonas PS, Sparrow D, Weiss ST, and Kelsey K. 2005b. Glutathione-S-transferase M1, obesity, statins, and autonomic effects of particles. *Am J Respir Crit Care Med* 172, 1529-33.
- Schwartz J. 2004a. The effects of particulate air pollution on daily deaths: a multi-city case crossover analysis. *Occup Environ Med* 61:956–61.
- Schwartz J. 2004b. Is the association of airborne particles with daily deaths confounded by gaseous air pollutants? An approach to control by matching. *Environ Health Perspect* 112:557–61.
- Schwartz J. 2001. Is there harvesting in the association of airborne particles with daily deaths and hospital admissions? *Epidemiology* 12: 55–61.
- Schwartz J. 2000. Harvesting and long term exposure effects in the relationship between air pollution and mortality. *Am. J. Epidemiol* 151: 440–8.
- Seagrave J, McDonald JD, Gigliotti AP, Nikula KJ, Seilkop SK, Gurevich M, and Mauderly JL. 2002. Mutagenicity and *in vivo* toxicity of combined particulate and semivolatile organic fractions of gasoline and diesel engine emissions. *Toxicol Sci* 70:212–26.

- Seagrave J, McDonald JD, Bedrick E, Edgerton ES, Gigliotti AP, Jansen JJ, Ke L, Naeher LP, Seilkop SK, Zheng M, and Mauderly JL. 2006. Lung toxicity of ambient particulate matter from southeastern U.S. sites with different contributing sources: relationships between composition and effects. *Environ Health Perspect* 114:1387–93.
- See SW and Balasubramanian R. 2006. Risk assessment of exposure to indoor aerosols associated with Chinese cooking. *Environ Res* 102:197–204.
- Segala C, Poizeau D, Neukirch F, Aubier M, Samson J, and Gehanno P. 2004. Air pollution, passive smoking, and respiratory symptoms in adults. *Arch Environ Health* 59:669–76.
- Semmler M, Seitz J, Erbe F, Mayer P, Heyder J, Oberdörster G, and Kreyling WG. 2004. Long-term clearance kinetics of inhaled ultrafine insoluble iridium particles from the rat lung, including transient translocation into secondary organs. *Inhal Toxicol* 16:453–9.
- Shao L, Shi Z, Jones TP, Li J, Whittaker AG, and Berube KA. 2006. Bioreactivity of particulate matter in Beijing air: results from plasmid DNA assay. *Sci Total Environ* 367:261–72.
- Sharma M, Kumar VN, Katiyar SK, Sharma R, Shukla BP, and Sengupta B. 2004. Effects of particulate air pollution on the respiratory health of subjects who live in three areas in Kanpur, India. *Arch Environ Health* 59:348–58.
- Sheppard L, Slaughter JC, Schildcrout J, Liu LJS, and Lumley T. 2005. Exposure and measurement contributions to estimates of acute air pollution effects. *J Expo Analysis Environ Epidemiol* 15:366–76.
- Shi H, Kleinstreuer C, Zhang Z, and Kim CS. 2004. Nanoparticle transport and deposition in bifurcating tubes with different inlet conditions 16:2199–211.
- Shi T, Knaapen AM, Begerow J, Birmili W, Borm PJ, and Schins RP. 2003. Temporal variation of hydroxyl radical generation and 8-hydroxy-2'-deoxyguanosine formation by coarse and fine particulate matter. *Occup Environ Med* 60:315–21.
- Shi T, Duffin R, Borm PJ, Li H, Weishaupt C, and Schins RP. 2006. Hydroxyl-radical-dependent DNA damage by ambient particulate matter from contrasting sampling locations. *Environ Res* 101:18–24.
- Shwe TT, Yamamoto S, Kakeyama M, Kobayashi T, and Fujimaki H. 2005. Effect of intratracheal instillation of ultrafine carbon black on proinflammatory cytokine and chemokine release and mRNA expression in lung and lymph nodes of mice. *Toxicol Appl Pharmacol* 209:51–61.
- Shwe TTW, Yamamoto S, Ahmed S, Kakeyama M, Kobayashi T, and Fujimaki H. 2006. Brain cytokine and chemokine mRNA expression in mice induced by intranasal instillation with ultrafine carbon black. *Toxicol Lett* 163:153–60.
- Silkoff PE, Zhang L, Dutton S, Langmack EL, Vedal S, Murphy J, and Make B. 2005. Winter air pollution and disease parameters in advanced chronic obstructive pulmonary disease panels residing in Denver, Colorado. *J Allergy Clin Immunol* 115:337–44.
- Silva VM, Corson N, Elder A, and Oberdörster G. 2005. The rat ear vein model for investigating *in vivo* thrombogenicity of ultrafine particles (UFP). *Toxicol Sci* 85:983–9.
- Simpson R, Williams G, Petroschevsky A, Best T, Morgan G, Denison L, Hinwood A, Neville G, and Neller A. 2005. The short-term effects of air pollution on daily mortality in four Australian cities. *Aust N Z J Public Health* 29:205–12.

- Sinclair AH and Tolsma D. 2004. Associations and lags between air pollution and acute respiratory visits in an ambulatory care setting: 25-month results from the aerosol research and inhalation epidemiological study. *J Air Waste Manag Assoc* 54:1212–18.
- Sioutas C, Delfino RJ, and Singh M. 2005. Exposure assessment for atmospheric ultrafine particles (UFPs) and implications in epidemiologic research. *Environ Health Perspect* 113:947–55.
- Sirivelu MP, MohanKumar SM, Wagner JG, Harkema JR, and MohanKumar PS. 2006. Activation of the stress axis and neurochemical alterations in specific brain areas by concentrated ambient particle exposure with concomitant allergic airway disease. *Environ Health Perspect* 114:870–4.
- Šišović A, Fugas M, and Sega K. 1996. Assessment of human inhalation exposure to polycyclic aromatic hydrocarbons. *J Expo Analysis Environ Epidemiol* 6:439–47.
- Slaughter JC, Lumley T, Sheppard L, Koenig JQ, and Shapiro GG. 2003. Effects of ambient air pollution on symptom severity and medication use in children with asthma. *Ann Allergy Asthma Immunol* 91:346–53.
- Slaughter JC, Kim E, Sheppard L, Sullivan JH, Larson TV, and Claiborn C. 2005. Association between particulate matter and emergency room visits, hospital admissions and mortality in Spokane, Washington. *J Expo Anal Environ Epidemiol* 15:153–9.
- Smith KR, Kim S, Recendez JJ, Teague SV, Menache MG, Grubbs DE, Sioutas C, and Pinkerton KE. 2003. Airborne particles of the California central valley alter the lungs of healthy adult rats. *Environ Health Perspect* 111:902–8; discussion A408–9.
- Soares SR, Bueno-Guimaraes HM, Ferreira CM, Rivero DH, De Castro I, Garcia ML, and Saldiva PH. 2003. Urban air pollution induces micronuclei in peripheral erythrocytes of mice *in vivo*. *Environ Res* 92:191–6.
- Soberanes S, Panduri V, Mutlu GM, Ghio A, Bundinger GR, and Kamp DW. 2006. p53 mediates particulate matter-induced alveolar epithelial cell mitochondria-regulated apoptosis. *Am J Respir Crit Care Med* 174:1229–38.
- Sodeman D.A., Toner S.M., and Prather K.A. 2005. Determination of single particle mass spectral signatures from light-duty vehicle emissions. *Environ Sci Technol* 39:4569–80.
- Sokol RZ, Kraft P, Fowler IM, Mamet R, Kim E, and Berhane KT. 2006. Exposure to environmental ozone alters semen quality. *Environ Health Perspect* 114:360–5.
- Solomon C, Poole J, Jarup L, Palmer K, and Coggon, D. 2003. Cardio-respiratory morbidity and long-term exposure to particulate air pollution. *Int J Environ Health Res* 13:327–35.
- Somers CM, Yauk CL, White PA, Parfett CL, and Quinn JS. 2002. Air pollution induces heritable DNA mutations. *Proc Natl Acad Sci USA* 99:15904–7.
- Somers CM, McCarry BE, Malek F, and Quinn JS. 2004. Reduction of particulate air pollution lowers the risk of heritable mutations in mice. *Science* 304:1008–10.
- Sørensen M, Daneshvar B, Hansen M, Dragsted LO, Hertel O, Knudsen L, and Loft S. 2003a. Personal PM_{2.5} exposure and markers of oxidative stress in blood. *Environ Health Perspect* 111:161–6.
- Sørensen M, Autrup H, Hertel O, Wallin H, Knudsen LE, and Loft S. 2003b. Personal exposure to PM_{2.5} and biomarkers of DNA damage. *Cancer Epidemiol Biomarkers Prev* 12:191–6.

- Sørensen M, Autrup H, Møller P, Hertel O, Jensen SS, Vinzents P, Knudsen LE, and Loft S. 2003c. Linking exposure to environmental pollutants with biological effects. *Mutat Res* 544:255–71.
- Sørensen M, Loft S, Andersen HV, Raaschou-Nielsen O, Skovgaard LT, Knudsen LE, Nielsen IV, and Hertel O. 2005a. Personal exposure to PM_{2.5}, black smoke and NO₂ in Copenhagen: relationship to bedroom and outdoor concentrations covering seasonal variation. *J Expo Analysis Environ Epidemiol* 15:413–22.
- Sørensen M, Schins RPF, Hertel O, and Loft S. 2005b. Transition metals in personal samples of PM_{2.5} and oxidative stress in human volunteers. *Cancer Epidemiol Biomarkers Prev* 14:1340–3.
- Sosnowski TR, Moskal A, and Gradon L. 2006. Dynamics of oropharyngeal aerosol transport and deposition with the realistic flow pattern. *Inhal Toxicol* 18:773–80.
- Spooner PM, Albert C, Benjamin EJ, Boineau R, Elston RC, George AL Jr, Jouven X, Kuller LH, MacCluer JW, Marban E, Muller JE, Schwartz PJ, Siscovick DS, Tracy RP, Zareba W, and Zipes DP. 2001. Sudden cardiac death, genes, and arrhythmogenesis: consideration of new population and mechanistic approaches from a national heart, lung, and blood institute workshop, part I. *Circulation* 103:2361–4.
- Staniswalis JG, Parks NJ, Bader JO, and Maldonado YM. 2005. Temporal analysis of airborne particulate matter reveals a dose-rate effect on mortality in El Paso: indications of differential toxicity for different particle mixtures. *J Air Waste Manag Assoc* 55:893–902.
- Steenenberg PA, Bischoff EW, de Klerk A, Verlaan AP, Jongbloets LM, van Loveren H, Opperhuizen A, Zomer G, Heisterkamp SH, Hady M, Spijksma FT, Fischer PH, Dormans JA, and van Amsterdam JG. 2003. Acute effect of air pollution on respiratory complaints, exhaled NO and biomarkers in nasal lavages of allergic children during the pollen season. *Int Arch Allergy Immunol* 131:127–37.
- Steenenberg P, Verlaan A, De Klerk A, Boere A, Loveren H, and Cassee F. 2004a. Sensitivity to ozone, diesel exhaust particles, and standardized ambient particulate matter in rats with a listeria monocytogenes-induced respiratory infection. *Inhal Toxicol* 16:311–17.
- Steenenberg PA, Withagen CE, van Dalen WJ, Dormans JA, Cassee FR, Heisterkamp SH, and van Loveren H. 2004b. Adjuvant activity of ambient particulate matter of different sites, sizes, and seasons in a respiratory allergy mouse model. *Toxicol Appl Pharmacol* 200:186–200.
- Steenenberg PA, Withagen CE, van Dalen WJ, Dormans JA, and van Loveren H. 2004c. Adjuvant activity of ambient particulate matter in macrophage activity-suppressed, N-acetylcysteine-treated, iNOS- and IL-4-deficient mice. *Inhal Toxicol* 16:835–43.
- Steenenberg PA, Withagen CE, van Dalen WJ, Dormans JA, Heisterkamp SH, van Loveren H, and Cassee FR. 2005. Dose dependency of adjuvant activity of particulate matter from five European sites in three seasons in an ovalbumin-mouse model. *Inhal Toxicol* 17:133–45.
- Steenenberg PA, van Amelsvoort L, Lovik M, Hetland RB, Alberg T, Halatek T, Bloemen HJ, Rydzynski K, Swaen G, Schwarze P, Dybing E, and Cassee FR. 2006. Relation between sources of particulate air pollution and biological effect parameters in samples from four European cities: an exploratory study. *Inhal Toxicol* 18:333–46.
- Stieb DM, Brook JR, Broder I, Judek S, Burnett RT, and Beveridge RC. 1998. Personal exposure of adults with cardiorespiratory disease to particulate acid and sulfate in Saint John, New Brunswick, Canada. *Appl Occup Environ Hyg* 13:461–8.

- Stieb DM, Judek S, and Burnett RT. 2002. Meta-analysis of time-series studies of air pollution and mortality: effects of gases and particles and the influence of cause of death, age, and season. *J Air Waste Manag Assoc* 52:470–84.
- Stieb DM, Judek S, and Burnett RT. 2003. Meta-analysis of time-series studies of air pollution and mortality: update in relation to the use of generalized additive models. *J Air Waste Manag Assoc* 53:258–61.
- Stoeger T, Reinhard C, Takenaka S, Schroepfel A, Karg E, Ritter B, Heyder J, and Schulz H. 2006. Instillation of six different ultrafine carbon particles indicates a surface area threshold dose for acute lung inflammation in mice. *Environ Health Perspect* 114:328–33.
- Stolzel M, Breitner S, Cyrus J, Pitz M, Wolke G, Kreyling W, Heinrich J, Wichmann HE, and Peters A. 2007. Daily mortality and particulate matter in different size classes in Erfurt, Germany. *J Expo Sci Environ Epidemiol* 17:458–67 (pre-published online in 2006).
- Strand M, Vedal S, Rodes C, Dutton SJ, Gelfand EW, and Rabinovitch N. 2006. Estimating effects of ambient PM(2.5) exposure on health using PM(2.5) component measurements and regression calibration. *J Expo Sci Environ Epidemiol* 16:30–8.
- Sturm R and Hofmann W. 2004. Stochastic simulation of alveolar particle deposition in lungs affected by different types of emphysema. *J Aerosol Med* 17:357–72.
- Su Y, Lei YD, Wania F, Shoeib M, and Harner T. 2006. Regressing gas/particle partitioning data for polycyclic aromatic hydrocarbons. *Environ Sci Technol* 40:3558–64.
- Sugiri D, Ranft U, Schikowski T, and Kramer U. 2006. The influence of large-scale airborne particle decline and traffic-related exposure on children's lung function. *Environ Health Perspect* 114:282–8.
- Suh HH, Koutrakis P, and Spengler JD. 1993a. Indoor and outdoor acid aerosol and gas concentrations. *In: Jantunen M, Kalliokoski P, Kukkonen E, Saarela K, Seppänen O, Vuorelma, H, eds. Indoor air '93: proceedings of the 6th international conference on indoor air quality and climate. Volume 3: combustion products, risk assessment, policies; July; Helsinki, Finland. Helsinki, Finland: Indoor Air* 3:257–62.
- Suh HH, Koutrakis P, and Spengler JD. 1993b. Validation of personal exposure models for sulfate and aerosol strong acidity. *J Air Waste Manage Assoc* 43:845–50.
- Suh HH, Spengler JD, and Koutrakis P. 1992. Personal exposures to acid aerosols and ammonia. *Environ Sci Technol* 26:2507–17.
- Sullivan J, Ishikawa N, Sheppard L, Siscovick D, Checkoway H, and Kaufman J. 2003. Exposure to ambient fine particulate matter and primary cardiac arrest among persons with and without clinically recognized heart disease. *Am J Epidemiol* 157:501–9.
- Sullivan J, Sheppard L, Schreuder A, Ishikawa N, Siscovick D, and Kaufman J. 2005a. Relation between short-term fine-particulate matter exposure and onset of myocardial infarction. *Epidemiology* 16:41–8.
- Sullivan JH, Schreuder AB, Trenga CA, Liu SL, Larson TV, Koenig JQ, and Kaufman JD. 2005b. Association between short term exposure to fine particulate matter and heart rate variability in older subjects with and without heart disease. *Thorax* 60:462–6.
- Sun H-L, Chou M-C, and Lou KH. 2006. The relationship of air pollution to ED visits for asthma differ between children and adults. *Am J Emerg Med* 24:709–13.

Sun QMP, Aixia Wang B, Ximei Jin B, Alex Natanzon M, Damon Duquaine M, Robert D. Brook M, Juan-Gilberto S. Aguinaldo M, Zahi A. Fayad P, Valentin Fuster MP, Morton Lippmann P, Lung Chi Chen P, and Sanjay Rajagopalan M. 2005. Long-term air pollution exposure and acceleration of atherosclerosis and vascular inflammation in an animal model. *JAMA* 294:3003–10.

Symons JM, Wang L, Guallar E, Howell E, Dominici F, Schwab M, Ange BA, Samet J, Ondov J, Harrison D, and Geyh A. 2006. A case-crossover study of fine particulate matter air pollution and onset of congestive heart failure symptom exacerbation leading to hospitalization. *Am J Epidemiol* 164:421–33.

Tager IB, Balmes J, Lurmann F, Ngo L, Alcorn S, and Kunzli N. 2005. Chronic exposure to ambient ozone and lung function in young adults. *Epidemiology* 16:751–9.

Takenaka S, Karg E, Kreyling WG, Lentner B, Schulz H, Ziesenis A, Schramel P, and Heyder J. 2004. Fate and toxic effects of inhaled ultrafine cadmium oxide particles in the rat lung. *Inhal Toxicol* 16 Suppl 1:83–92.

Takenaka S, Karg E, Kreyling WG, Lentner B, Moller W, Behnke-Semmler M, Jennen L, Walch A, Michalke B, Schramel P, Heyder J, and Schulz H. 2006. Distribution pattern of inhaled ultrafine gold particles in the rat lung. *Inhal Toxicol* 18:733–40.

Tamaoki J, Isono K, Takeyama K, Tagaya E, Nakata J, and Nagai A. 2004. Ultrafine carbon black particles stimulate proliferation of human airway epithelium via EGF receptor-mediated signaling pathway. *Am J Physiol Lung Cell Mol Physiol* 287:L1127–33.

Tankersley CG, Shank JA, Flanders SE, Soutiere SE, Rabold R, Mitzner W, and Wagner EM. 2003. Changes in lung permeability and lung mechanics accompany homeostatic instability in senescent mice. *J Appl Physiol* 95:1681–7.

Tankersley CG, Campen M, Bierman A, Flanders SE, Broman KW, and Rabold R. 2004. Particle effects on heart-rate regulation in senescent mice. *Inhal Toxicol* 16:381–90.

Tao F and Kobzik L. 2002. Lung macrophage-epithelial cell interactions amplify particle-mediated cytokine release. *Am J Respir Cell Mol Biol* 26:499–505.

Thatcher TL, Lai ACK, Moreno-Jackson R, Sextro RG, and Nazaroff WW. 2002. Effects of room furnishings and air speed on particle deposition rates indoors. *Atmos Env* 36:1811–19.

Thatcher TL, Lunden MM, Revzan KL, Sextro RG, and Brown NJ. 2003. A concentration rebound method for measuring particle penetration and deposition in the indoor environment. *Aerosol Sci Tech* 37:847–64.

Thomson E, Kumarathasan P, Goegan P, Aubin RA, and Vincent R. 2005. Differential regulation of the lung endothelin system by urban particulate matter and ozone. *Toxicol Sci* 88:103–13.

Thornburg J, Ensor DS, Rodes CE, Lawless PA, Sparks LE, and Mosley RB. 2001. Penetration of particles into buildings and associated physical factors. Part 1: model development and computer simulations. *Aerosol Sci Tech* 34:284–96.

Thornburg JW, Rodes CE, Lawless PA, Steven CD, and Williams RW. 2004. A pilot study of the influence of residential HAC duty cycle on indoor air quality. *Atmos Env* 38:1567–77.

Timonen KL, Hoek G, Heinrich J, Bernard A, Brunekreef B, de Hartog J, Hameri K, Ibaldo-Mulli A, Mirme A, Peters A, Tiittanen P, Kreyling WG, and Pekkanen J. 2004. Daily variation in fine and ultrafine particulate air pollution and urinary concentrations of lung Clara cell protein CC16. *Occup Environ Med* 61:908–14.

- Timonen KL, Vanninen E, de Hartog J, Ibaldo-Mulli A, Brunekreef B, Gold DR, Heinrich J, Hoek G, Lanki T, Peters A, Tarkiainen T, Tiittanen P, Kreyling W, and Pekkanen J. 2006. Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease: The ULTRA study. *J Expo Sci Environ Epidemiol* 16:332–41.
- Toivola M, Nevalainen A, and Alm S. 2004. Personal exposures to particles and microbes in relation to microenvironmental concentrations. *Indoor Air* 14:351–9.
- Tong Y, Zhang G, Li Y, Tan M, Wang W, Chen J, Hwu Y, Hsu PC, Je JH, Margaritondo G, Song W, Jiang R, and Jiang Z. 2006. Synchrotron microradiography study on acute lung injury of mouse caused by PM (2.5) aerosols. *Eur J Radiol* 58:266–72.
- Tonne CC, Whyatt RM, Camann DE, Perera FP, and Kinney PL. 2004. Predictors of personal polycyclic aromatic hydrocarbon exposures among pregnant minority women in New York City. *Environ Health Perspect* 112:754–9.
- Touloumi G, Atkinson R, Le Tertre A, Samoli E, Schwartz J, Schindler C, Vonk JM, Rossi G, Saez N, Rabzenko D, and Katsouyanni K. 2004. Analysis of health outcome time series data in epidemiological studies. *Environmetrics* 15:101–17.
- Touloumi G, Samoli E, Quenel P, Paldy A, Anderson RH, Zmirou D, Galan I, Forsberg B, Schindler C, Schwartz J, and Katsouyanni K. 2005. Short-term effects of air pollution on total and cardiovascular mortality: the confounding effect of influenza epidemics. *Epidemiology* 16:49–57.
- Tovalin H, Valverde M, Morandi MT, Blanco S, Whitehead L, and Rojas E. 2006. DNA damage in outdoor workers occupationally exposed to environmental air pollutants. *Occup Environ Med* 63:230–6.
- Trenga CA, Sullivan JH, Schildcrout JS, Shepherd KP, Shapiro GG, Liu LJ, Kaufman JD, and Koenig JQ. 2006. Effect of particulate air pollution on lung function in adult and pediatric subjects in a Seattle panel study. *Chest* 129:1614–22.
- Tsai SS, Huang CH, Goggins WB, Wu TN, and Yang CY. 2003a. Relationship between air pollution and daily mortality in a tropical city: Kaohsiung, Taiwan. *J Toxicol Environ Health A* 66:1341–9.
- Tsai SS, Goggins WB, Chiu HF, and Yang CY. 2003b. Evidence for an association between air pollution and daily stroke admissions in Kaohsiung, Taiwan. *Stroke* 34:2612–6.
- Tsai SS, Chen CC, Hsieh HJ, Chang CC, and Yang CY. 2006a. Air pollution and postneonatal mortality in a tropical city: Kaohsiung, Taiwan. *Inhal Toxicol* 18:185–9.
- Tsai SS, Cheng MH, Chiu HF, Wu TN, and Yang CY. 2006b. Air pollution and hospital admissions for asthma in a tropical city: Kaohsiung, Taiwan. *Inhal Tox* 18:549–54.
- Tung TCW and Chao CYHBJ. 1999. A methodology to investigate the particulate penetration coefficient through building shell. *Atmos Env* 33:881–93.
- United States Environmental Protection Agency (US EPA). 1996. Air Quality Criteria for Particulate Matter. Washington, DC: Publication No. EPA 600/P-95/001aF-bF-cF.
- United States Environmental Protection Agency (US EPA). 2004. Air Quality Criteria for Particulate Matter. Washington, DC: Publication No. EPA 600/P-99/002aF-bF.
- United States Environmental Protection Agency (US EPA). 2005. Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information. OAQPS Staff Paper EPA 452/R-05-005a.

- United States Environmental Protection Agency. 2006. Air Quality Criteria for Ozone and Related Photochemical Oxidants. Washington, DC: Publication No. EPA 600/R-5/004aF.
- Upadhyay D, Panduri V, Ghio A, and Kamp DW. 2003. Particulate matter induces alveolar epithelial cell DNA damage and apoptosis: role of free radicals and the mitochondria. *Am J Respir Cell Mol Biol* 29:180–7.
- Urch B, Brook JR, Wasserstein D, Brook RD, Rajagopalan S, Corey P, and Silverman F. 2004. Relative contributions of PM_{2.5} chemical constituents to acute arterial vasoconstriction in humans. *Inhal Toxicol* 16:345–52.
- Urch B, Silverman F, Corey P, Brook JR, Lukic KZ, Rajagopalan S, and Brook RD. 2005. Acute blood pressure responses in healthy adults during controlled air pollution exposures. *Environ Health Perspect* 113:1052–55.
- Vajanapoom N, Shy CM, Neas LM, and Loomis D. 2002. Associations of particulate matter and daily mortality in Bangkok, Thailand. *Southeast Asian J Trop Med Public Health* 33:389–99.
- Vallejo M, Ruiz S, Hermosillo AG, Borja-Aburto VH, and Cardenas M. 2006. Ambient fine particles modify heart rate variability in young healthy adults. *J Expo Sci Environ Epidemiol* 16:125–30.
- Van Roosbroeck S, Wichmann J, Janssen NAH, Hoek G, van Wijnen JH, Lebret E, and Brunekreef B. 2006. Long-term personal exposure to traffic-related air pollution among school children, a validation study. *Sci Total Env* 368:565–73.
- Vedal S, Brauer M, White R, and Petkau J. 2003. Air pollution and daily mortality in a city with low levels of pollution. *Environ Health Perspect* 111:45–52.
- Vedal S, Rich K, Brauer M, White R, and Petkau J. 2004. Air pollution and cardiac arrhythmias in patients with implantable cardioverter defibrillators. *Inhal Toxicol* 16:353–62.
- Vegni FE and Ros O. 2004. Hospital accident and emergency burden is unaffected by today's air pollution levels. *Eur J Emerg Med* 11:86–8.
- Vegni FE, Castelli B, Auxilia F, and Wilkinson P. 2005. Air pollution and respiratory drug use in the city of Como, Italy. *Eur J Epidemiol* 20:351–8.
- Venners SA, Wang B, Xu Z, Schlatter Y, Wang L, and Xu X. 2003. Particulate matter, sulfur dioxide, and daily mortality in Chongqing, China. *Environ Health Perspect* 111:562–7.
- Veranth JM, Reilly CA, Veranth MM, Moss TA, Langelier CR, Lanza DL, and Yost GS. 2004. Inflammatory cytokines and cell death in BEAS-2B lung cells treated with soil dust, lipopolysaccharide, and surface-modified particles. *Toxicol Sci* 82:88–96.
- Veranth JM, Moss TA, Chow JC, Labban R, Nichols WK, Walton JC, Watson JG, and Yost GS. 2006. Correlation of *in vitro* cytokine responses with the chemical composition of soil-derived particulate matter. *Environ Health Perspect* 114:341–9.
- Veronesi B, Makwana O, Pooler M, and Chen LC. 2005. Effects of subchronic exposures to concentrated ambient particles. VII. Degeneration of dopaminergic neurons in Apo E^{-/-} mice. *Inhal Toxicol* 17:235–41.
- Vette AF, Rea AW, Lawless PA, Rodes CE, Evans G, Highsmith VR, and Sheldon L. 2001. Characterization of indoor–outdoor aerosol concentration relationships during the Fresno PM exposure studies. *Aerosol Sci Tech* 34:118–26.

- Villeneuve PJ, Burnett RT, Shi Y, Krewski D, Goldberg MS, Hertzman C, Chen Y, and Brook J. 2003. A time-series study of air pollution, socioeconomic status, and mortality in Vancouver, Canada. *J Expo Anal Environ Epidemiol* 13:427–35.
- Villeneuve PJ, Chen L, Stieb D, and Rowe BH. 2006a. Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. *Eur J Epidemiol* 21:689–700.
- Villeneuve PJ, Doiron MS, Stieb D, Dales R, Burnett RT, and Dugandzic R. 2006b. Is outdoor air pollution associated with physician visits for allergic rhinitis among the elderly in Toronto, Canada? *Allergy* 61:750–8.
- Vinzents PS, Moller P, Sørensen M, Knudsen LE, Hertel O, Jensen FP, Schibye B, and Loft S. 2005. Personal exposure to ultrafine particles and oxidative DNA damage. *Environ Health Perspect* 113:1485–90.
- Vogel CF, Sciuolo E, Wong P, Kuzmicky P, Kado N, and Matsumura F. 2005. Induction of proinflammatory cytokines and C-reactive protein in human macrophage cell line U937 exposed to air pollution particulates. *Environ Health Perspect* 113:1536–41.
- Volpino P, Tomei F, La Valle C, Tomao E, Rosati MV, Ciarrocca M, De Sio S, Cangemi B, Vigliarolo R, and Fedele F. 2004. Respiratory and cardiovascular function at rest and during exercise testing in a healthy working population: effects of outdoor traffic air pollution. *Occup Med (Lond)* 54:475–82.
- von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti D, Elosua R, Hormann A, Kulmala M, Lanki T, Lowel H, Pekkanen J, Picciotto S, Sunyer J, and Forastiere F. 2005. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. *Circulation* 112:3073–9.
- Voutilainen A, Kaipio JP, Pekkanen J, Timonen KL, and Ruuskanen J. 2004. Theoretical analysis of the influence of aerosol size distribution and physical activity on particle deposition pattern in human lungs. *Scand J Work Environ Health* 30 (Suppl 2):73–9.
- Waldman JM, Liroy PJ, Greenberg A, and Butler JP. 1991. Analysis of human exposure to benzo(a) pyrene via inhalation and food ingestion in the total human environmental exposure study (THEES). *J Expo Analysis Environ Epidemiol* 1:193–225.
- Wallace L. 1996. Indoor particles: a review. *J Air Waste Man 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.
- Wallace LA. 2006. Personal monitors. *In Exposure Analysis*. WR Ott et al., editors. Boca Raton, FL: CRC Press. p. 99–112.
- Wallace L and Howard-Reed C. 2002. Continuous monitoring of ultrafine, fine, and coarse particles in a residence for 18 months in 1999–2000. *J Air Waste Man Assoc* 52:828–44.
- Wallace L and Williams R. 2005. Use of personal–indoor–outdoor sulfur concentrations to estimate the infiltration factor and outdoor exposure factor for individual homes and persons. *Environ Sci Technol* 39:1707–14.
- Wallace LA, Emmerich SJ, and 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 Expo Analysis Environ Epidemiol* 12:296–306.
- Wallace LA, Mitchell H, O'Connor GT, Neas L, Lippmann M, Kattan M, Koenig J, Stout JW, Vaughn BJ, Wallace D, Walter M, Adams K, and Liu LJS. 2003a. Particle concentrations in

inner-city homes of children with asthma: the effect of smoking, cooking, and outdoor pollution. *Environ Health Perspect* 111:1265–72.

Wallace LA, Williams RW, Suggs J, Sheldon L, Zweidinger R, Rea AW, Vette A, Leovic KW, Norris G, Landis M, Stevens CD, Corner T, Croghan C, Rodes C, Lawless PA, Thornburg J, Liu L-JS, Allen R, Kalman D, Kaufman J, Koenig J, Larson T, Lumley T, Sheppard L, Brown K, Sarnat J, Suh H, Wheeler A, and Koutrakis P. 2003b. Exposure of high risk subpopulations to particles: final report (APM-21). Research Triangle Park, NC: National Exposure Research Laboratory, Office of Research and Development, US Environmental Protection Agency. Publication No. EPA 600/R-03/145.

Wallace LA, Emmerich SJ, and Howard-Reed C. 2004a. Effect of central fans and in-duct filters on deposition rates of ultrafine and fine particles in an occupied townhouse. *Atmos Env* 38:405–13.

Wallace LA, Emmerich SJ, and Howard-Reed C. 2004b. Source strengths of ultrafine and fine particles due to cooking with a gas stove. *Environ Sci Technol* 38:2304–11.

Wallace L, Williams R, Rea A, and Croghan C. 2006a. Continuous weeklong measurements of personal exposures and indoor concentrations of fine particles for 37 health-impaired North Carolina residents for up to four seasons. *Atmos Env* 40:399–414.

Wallace L, Williams R, Suggs J, and Jones P. 2006b. Estimating contributions of outdoor fine particles to indoor concentrations and personal exposures: effects of household characteristics and personal activities. Research Triangle Park, NC: National Exposure Research Laboratory, Office of Research and Development, US Environmental Protection Agency. Publication No. EPA 600/R-06/023.

Walters DM, Breyse PN, Schofield B, and Wills-Karp M. 2002. Complement factor 3 mediates particulate matter-induced airway hyperresponsiveness. *Am J Respir Cell Mol Biol* 27:413–18.

Wang CS. 2005. Inhaled Particles. *Interface Science and Technology Volume 5*. London, UK: Elsevier. 187 pp.

Wang X, Bi X, Sheng G, and Fu J. 2006. Hospital indoor $PM_{10}/PM_{2.5}$ and associated trace elements in Guangzhou, China. *Sci Total Env* 366:124–35.

Watson JG, Chow JC and Chen L-WA. 2005. Summary of organic and elemental/black carbon analysis methods and intercomparisons. *Aerosol Air Qual Res* 5:69–109.

Watson JG, Chow JC, Lowenthal DH, Pritchett LC, Frazier CA, Neuroth GR and Robbins R. 1994. Differences in the carbon composition of source profiles for diesel- and gasoline-powered vehicles. *Atmos Env* 28:2493–505.

Wei A and Meng Z. 2006a. Evaluation of micronucleus induction of sand dust storm fine particles ($PM_{2.5}$) in human blood lymphocytes. *Environmental Toxicology and Pharmacology* 22, 292–297.

Wei A and Meng Z. 2006b. Induction of chromosome aberrations in cultured human lymphocytes treated with sand dust storm fine particles ($PM_{2.5}$). *Toxicol Lett* 166:37–43.

Weisel CP, Zhang J, Turpin BJ, Morandi MT, Colome S, Stock TH, and Spektor DM. 2005. Relationships of Indoor, Outdoor, and Personal Air (RIOPA). Part I, Collection Methods and Descriptive Analyses. Boston, MA: Health Effects Institute, Research Report No. 130-1 and Houston, TX: Mickey Leland National Urban Air Toxics Research Center, Research Report No. 7.

- Wellenius GA, Saldiva PH, Batalha JR, Krishna Murthy GG, Coull BA, Verrier RL, and Godleski JJ. 2002. Electrocardiographic changes during exposure to residual oil fly ash (ROFA) particles in a rat model of myocardial infarction. *Toxicol Sci* 66:327–35.
- Wellenius GA, Coull BA, Godleski JJ, Koutrakis P, Okabe K, Savage ST, Lawrence JE, Murthy GG, and Verrier RL. 2003. Inhalation of concentrated ambient air particles exacerbates myocardial ischemia in conscious dogs. *Environ Health Perspect* 111:402–8.
- Wellenius GA, Batalha JR, Diaz EA, Lawrence J, Coull BA, Katz T, Verrier RL, and Godleski JJ. 2004. Cardiac effects of carbon monoxide and ambient particles in a rat model of myocardial infarction. *Toxicol Sci* 80:367–76.
- Wellenius GA, Bateson TF, Mittleman MA, and Schwartz J. 2005a. Particulate air pollution and the rate of hospitalization for congestive heart failure among medicare beneficiaries in Pittsburgh, Pennsylvania. *Am J Epidemiol* 161:1030–6.
- Wellenius GA, Schwartz J, and Mittleman MA. 2005b. Air pollution and hospital admissions for ischemic and hemorrhagic stroke among Medicare beneficiaries. *Stroke* 36:2549–53.
- Wellenius GA, Mittleman MA, and Schwartz J. 2006. Particulate air pollution and hospital admissions for congestive heart failure in seven United States cities. *Am J Cardiol* 97:404–8.
- Welty LJ and Zeger SL. 2005. Are the acute effects of particulate matter on mortality in the National Morbidity, Mortality, and Air Pollution Study the result of inadequate control for weather and season? A sensitivity analysis using flexible distributed lag models. *Am J Epidemiol* 162:80–8.
- Westerdahl D, Fruin S, Sax T, Fine PM, and Sioutas C. 2005. Mobile platform measurements of ultrafine particles and associated pollutant concentrations on freeways and residential streets in Los Angeles. *Atmos Env* 39:3597–610.
- Wheeler A, Zanobetti A, Gold DR, Schwartz J, Stone P, and Suh HH. 2006. The relationship between ambient air pollution and heart rate variability differs for individuals with heart and pulmonary disease. *Environ Health Perspect* 114:560–6.
- Wheeler AJ, Williams I, Beaumont RA, and Hamilton RS. 2000. Characterisation of particulate matter sampled during a study of children's personal exposure to airborne particulate matter in a UK urban environment. *Environ Monit Assess* 65:69–77.
- Wichers LB, Nolan JP, Winsett DW, Ledbetter AD, Kodavanti UP, Schladweiler MC, Costa DL, and Watkinson WP. 2004a. Effects of instilled combustion-derived particles in spontaneously hypertensive rats. Part I: Cardiovascular responses. *Inhal Toxicol* 16:391–405.
- Wichers LB, Nolan JP, Winsett DW, Ledbetter AD, Kodavanti UP, Schladweiler MC, Costa DL, and Watkinson WP. 2004b. Effects of instilled combustion-derived particles in spontaneously hypertensive rats. Part II: Pulmonary responses. *Inhal Toxicol* 16:407–19.
- Wichers LB, Ledbetter AD, McGee JK, Kellogg RB, Rowan WH, Nolan JP, Costa DL, and Watkinson WP. 2006. A method for exposing rodents to resuspended particles using whole-body plethysmography. *Part Fibre Toxicol* 3:12.
- Wichmann J, Janssen NAH, van der Zee S, and Brunekreef B. 2005. Traffic-related differences in indoor and personal absorption coefficient measurements in Amsterdam, the Netherlands. *Atmos Env* 39:7384–92.
- Wiebert P, Sanchez-Crespo A, Falk R, Philipson K, Lundin A, Larsson S, Moller W, Kreyling WG, and Svartengren M. 2006a. No significant translocation of inhaled 35-nm carbon particles to the circulation in humans. *Inhal Toxicol* 18:741–7.

- Wiebert P, Sanchez-Crespo A, Seitz J, Falk R, Philipson K, Kreyling WG, Moller W, Sommerer K, Larsson S, and Svartengren M. 2006b. Negligible clearance of ultrafine particles retained in healthy and affected human lungs. *Eur Respir J* 28:286–90.
- Wilhelm M and Ritz B. 2003. Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994–1996. *Environ Health Perspect* 111:207–16.
- Wilhelm M and Ritz B. 2005. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. *Environ Health Perspect* 113:1212–21.
- Williams R, Creason J, Zweidinger R, Watts R, Sheldon L, and Shy C. 2000a. Indoor, outdoor and personal exposure monitoring of particulate air pollution: The Baltimore elderly epidemiology–exposure pilot study. *Atmos Env* 34:4193–204.
- Williams R, Suggs J, Zweidinger R, Evans G, Creason J, Kwok R, Roders C, Lawless P, and Sheldon L. 2000b. The 1998 Baltimore Particulate Matter Epidemiology–Exposure Study: part 1. Comparison of ambient, residential outdoor, indoor and apartment particulate matter monitoring. *J Expo Analysis Environ Epidemiol* 10:518–32.
- Williams R, Suggs J, Creason J, Rodes C, Lawless P, Kwok R, Zweidinger R, and Sheldon L. 2000c. The 1998 Baltimore Particulate Matter Epidemiology–Exposure Study: part 2. Personal exposure assessment associated with an elderly study population. *J Expo Analysis Environ Epidemiol* 10:533–43.
- Williams R, Suggs J, Rodes C, Lawless P, Zweidinger R, Kwok R, Creason J, and Sheldon L. 2000d. Comparison of PM_{2.5} and PM₁₀ monitors. *J Expo Analysis Environ Epidemiol* 10:497–505.
- Williams R, Wallace L, Suggs J, Evans G, Creason J, Highsmith R, Sheldon L, Rea A, Vette A, Zweidinger R, Leovic K, Norris G, Landis M, Stevens C, Howard-Reed C, Conner T, Rodes C, Lawless P, Thornburg J, Liu L-JS, Kalman D, Kaufman J, Koenig J, Larson T, Lumley T, Sheppard L, Brown K, Suh H, Wheeler A, Gold D, Koutrakis P, and Lippmann M. 2002. Preliminary particulate matter mass concentrations associated with longitudinal panel studies: assessing human exposures of high risk subpopulations to particulate matter. Washington, DC: US Environmental Protection Agency. Publication No. EPA/60D/R-01/086.
- Williams R, Suggs J, Rea A, Leovic K, Vette A, Croghan C, Sheldon L, Rodes C, Thornburg J, Ejire A, Herbst M, and Sanders W. 2003a. The Research Triangle Park particulate matter panel study: PM mass concentration relationships. *Atmos Env* 37:5349–63.
- Williams R, Suggs J, Rea A, Sheldon L, Rodes C, and Thornburg J. 2003b. The Research Triangle Park particulate matter panel study: modeling ambient source contribution to personal and residential PM mass concentrations. *Atmos Env* 37:5365–78.
- Wilson JG, Kingham S, Pearce J, and Sturman AP. 2005. A review of intraurban variations in particulate air pollution: Implications for epidemiological research. *Atmos Env* 39:6444–62.
- Wilson MR, Lightbody JH, Donaldson K, Sales J, and Stone V. 2002. Interactions between ultrafine particles and transition metals *in vivo* and *in vitro*. *Toxicol Appl Pharmacol* 184:172–9.
- Wilson WE and Suh HH. 1997. Fine particles and coarse particles: concentration relationships relevant to epidemiologic studies. *J Air Waste Man Assoc* 47:1238–49.
- Wilson WE and Brauer M. 2006. Estimation of ambient and non-ambient components of particulate matter exposure from a personal monitoring panel study. *J Expo Sci Environ Epidemiol* 16:264–74.

- Wilson WE, Mage DT, and Grant LD. 2000. Estimating separately personal exposure to ambient and nonambient particulate matter for epidemiology and risk assessment: why and how. *J Air Waste Man Assoc* 50:1167–83.
- Wold LE, Simkhovich BZ, Kleinman MT, Nordlie MA, Dow JS, Sioutas C, and Kloner RA. 2006. *In vivo* and *in vitro* models to test the hypothesis of particle-induced effects on cardiac function and arrhythmias. *Cardiovasc Toxicol* 6:69–78.
- Wong TW, Tam WS, Yu TS, and Wong AH. 2002. Associations between daily mortalities from respiratory and cardiovascular diseases and air pollution in Hong Kong, China. *Occup Environ Med* 59:30–5.
- Wong TW, Tam W, Yu IT, Wun YT, Wong AH, and Wong CM. 2006. Association between air pollution and general practitioner visits for respiratory diseases in Hong Kong. *Thorax* 61:585–91.
- Woodruff TJ, Parker JD, Kyle AD, and Schoendorf KC. 2003. Disparities in exposure to air pollution during pregnancy. *Environ Health Perspect* 111:942–6.
- Wottrich R, Diabate S, and Krug HF. 2004. Biological effects of ultrafine model particles in human macrophages and epithelial cells in mono- and co-culture. *Int J Hyg Environ Health* 207:353–61.
- Wu CF, Delfino RJ, Floro JN, Samimi BS, Quintana PJE, Kleinman MT, and Liu LJS. 2005a. Evaluation and quality control of personal nephelometers in indoor, outdoor and personal environments. *J Expo Analysis Environ Epidemiol* 15:99–110 (1–12).
- Wu C-F, Delfino RJ, Floro JN, Quintana PJE, Samimi BS, Kleinman MT, Allen RW, and Liu L-JS. 2005b. Exposure assessment and modeling of particulate matter for asthmatic children using personal nephelometers. *Atmos Env* 39:3457–69.
- Wu C-F, Jimenez J, Claiborn C, Gould T, Simpson CD, Larson T, and Liu L-JS. 2006a. Agricultural burning in Eastern Washington: Part II. Exposure assessment. *Atmos Env* 40:5379–92.
- Wu SP, Tao S, and Liu WX. 2006b. Particle size distributions of polycyclic aromatic hydrocarbons in rural and urban atmosphere of Tianjin, China. *Chemosphere* 62:357–67.
- Xia T, Korge P, Weiss JN, Li N, Venkatesen MI, Sioutas C, and Nel A. 2004. Quinones and aromatic chemical compounds in particulate matter induce mitochondrial dysfunction: implications for ultrafine particle toxicity. *Environ Health Perspect* 112:1347–58.
- Xia T, Kovoichich M, and Nel A. 2006. The role of reactive oxygen species and oxidative stress in mediating particulate matter injury. *Clin Occup Environ Med* 5:817–36.
- Yakovleva E, Hopke PK, and Wallace L. 1999. Receptor modeling assessment of particle total exposure assessment methodology data. *Environ Sci Technol* 33:3643–50.
- Yamamoto S, Tin-Tin-Win-Shwe, Ahmed S, Kobayashi T, and Fujimaki H. 2006. Effect of ultrafine carbon black particles on lipoteichoic acid-induced early pulmonary inflammation in BALB/c mice. *Toxicol Appl Pharmacol* 213:256–66.
- Yamawaki H and Iwai N. 2006. Mechanisms underlying nano-sized air-pollution-mediated progression of atherosclerosis: carbon black causes cytotoxic injury/inflammation and inhibits cell growth in vascular endothelial cells. *Circ J* 70:129–40.
- Yamazaki S, Nitta H, Ono M, Green J, and Fukuhara S. 2007. Intracerebral hemorrhage associated with hourly concentration of ambient particulate matter: case-crossover analysis. *Occup Environ Med* 64:17–24 (pre-published online in 2006).

- Yang CY, Tseng YT, and Chang CC. 2003. Effects of air pollution on birth weight among children born between 1995 and 1997 in Kaohsiung, Taiwan. *J Toxicol Environ Health A* 66:807–16.
- Yang CY, Chang CC, Chuang HY, Tsai SS, Wu TN, and Ho CK. 2004a. Relationship between air pollution and daily mortality in a subtropical city: Taipei, Taiwan. *Environ Int* 30:519–23.
- Yang C-Y, Ho S-C, Chen Y-S, and Yang C-H. 2004b. Relationship between ambient air pollution and hospital admissions for cardiovascular diseases in Kaohsiung, Taiwan. *J Tox Environ Health A* 67:483–93.
- Yang C-Y, Chen Y-S, Chiu H-F, and Goggins W-B. 2005. Effects of Asian dust storm events on daily stroke admissions in Taipei, Taiwan. *Environ Res* 99:79–84.
- Yang CY, Hsieh HJ, Tsai SS, Wu TN, and Chiu HF. 2006. Correlation between air pollution and postneonatal mortality in a subtropical city: Taipei, Taiwan. *J Toxicol Environ Health A* 69:2033–40.
- Yang HH, Chien SM, Chao MR, and Lin CC. 2005. Particle size distribution of polycyclic aromatic hydrocarbons in motorcycle exhaust emissions. *J Hazard Matter* 125:154–9.
- Yang Q, Chen Y, Krewski D, Burnett RT, Shi Y, and McGrail KM. 2005. Effect of short-term exposure to low levels of gaseous pollutants on chronic obstructive pulmonary disease hospitalizations. *Environ Res* 99:99–105.
- Zanobetti A and Schwartz J. 2005. The effect of particulate air pollution on emergency admissions for myocardial infarction: a multicity case-crossover analysis. *Environ Health Perspect* 113:978–82.
- Zanobetti A and Schwartz J. 2006. Air pollution and emergency admissions in Boston, MA. *J Epidemiol Commun Health* 60:890–5.
- 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, Aranguel Ruiz E, and Katsouyanni K. 2002. The temporal pattern of mortality responses to air pollution: a multicity assessment of mortality displacement. *Epidemiology* 13:87–93.
- Zanobetti A, Canner MJ, Stone PH, Schwartz J, Sher D, Eagan-Bengston E, Gates KA, Hartley LH, Suh H, and Gold DR. 2004. Ambient pollution and blood pressure in cardiac rehabilitation patients. *Circulation* 110:2184–9.
- Zanobetti A, Wand MP, Schwartz J, and Ryan LM. 2000. Generalized additive distributed lag models: quantifying mortality displacement. *Biostatistics* 2000: 279–92.
- Zareba W, Nomura A, and Couderc JP. 2001. Cardiovascular effects of air pollution: what to measure in ECG? *Environ Health Perspect* 109 Suppl 4:533–8.
- Zeger SL, Thomas D, Dominici F, Samet JM, Schwartz J, Dockery D, and Cohen A. 2000. Exposure measurement error in time-series studies of air pollution: concepts and consequences. *Environ Health Perspect* 108:419–26.
- Zeger SL, Dominici F and Samet J. 1999. Harvesting-resistant estimates of air pollution effects on mortality. *Epidemiology* 10:171–75.
- Zeka A and Schwartz J. 2004. Estimating the independent effects of multiple pollutants in the presence of measurement error: an application of a measurement-error-resistant technique. *Environ Health Perspect* 112:1686–90.

- Zeka A, Zanobetti A, and Schwartz J. 2005. Short term effects of particulate matter on cause specific mortality: effects of lags and modification by city characteristics. *Occup Environ Med* 62:718–25.
- Zeka A, Zanobetti A, and Schwartz J. 2006a. Individual-level modifiers of the effects of particulate matter on daily mortality. *Am J Epidemiol* 163:849–59.
- Zeka A, Sullivan JR, Vokonas PS, Sparrow D, and Schwartz J. 2006b. Inflammatory markers and particulate air pollution: characterizing the pathway to disease. *Int J Epidemiol* 35:1347–54.
- Zelikoff JT, Chen LC, Cohen MD, Fang K, Gordon T, Li Y, Nadziejko C, and Schlesinger RB. 2003. Effects of inhaled ambient particulate matter on pulmonary antimicrobial immune defense. *Inhal Toxicol* 15:131–50.
- Zhang JJ, Hu W, Wei F, Wu G, Korn LR, and Chapman RS. 2002. Children's respiratory morbidity prevalence in relation to air pollution in four Chinese cities. *Environ Health Perspect* 110:961–7.
- Zhang Q, Kusaka Y, Zhu X, Sato K, Mo Y, Kluz T, and Donaldson K. 2003. Comparative toxicity of standard nickel and ultrafine nickel in lung after intratracheal instillation. *J Occup Health* 45:23–30.
- Zhang Y and Finlay WH. 2005. Experimental measurements of particle deposition in three proximal lung bifurcation models with an idealized mouth-throat. *J Aerosol Med* 18:460–73.
- Zhang Z and Kleinstreuer C. 2004. Airflow structures and nano-particle deposition in a human upper airway model. *J Comput Physics* 198:178–210.
- Zhao WX, Hopke PK, Norris G, Williams R, and Paatero P. 2006. Source apportionment and analysis on ambient and personal exposure samples with a combined receptor model and an adaptive blank estimation strategy. *Atmos Env* 40:3788–801.
- Zhao X, Wan Z, Chen G, Zhu H, Jiang S, and Yao J. 2002. Genotoxic activity of extractable organic matter from urban airborne particles in Shanghai, China. *Mutat Res* 514:177–92.
- Zhou YM, Zhong CY, Kennedy IM, Leppert VJ, and Pinkerton KE. 2003a. Oxidative stress and NFkappaB activation in the lungs of rats: a synergistic interaction between soot and iron particles. *Toxicol Appl Pharmacol* 190:157–69.
- Zhou YM, Zhong CY, Kennedy IM, and Pinkerton KE. 2003b. Pulmonary responses of acute exposure to ultrafine iron particles in healthy adult rats. *Environ Toxicol* 18:227–35.
- Zhu Y, Hinds WC, Kim S, Shen S, and Sioutas C. 2002a. Study of ultrafine particles near a major highway with heavy-duty diesel traffic. *Atmos Env* 36:4323–35.
- Zhu Y, Hinds WC, Kim S, and Sioutas C. 2002b. Concentration and size distribution of ultrafine particles near a major highway. *J Air Waste Man Assoc* 52:1032–42.
- Zhu Y, Hinds WC, Krudysz M, Kuhn T, Froines J, and Sioutas C. 2005. Penetration of freeway ultrafine particles into indoor environments. *J Aerosol Sci* 36:303–22.
- Zhu Y, Kuhn T, Mayo P, and Hinds WC. 2006. Comparison of daytime and nighttime concentration profiles and size distributions of ultrafine particles near a major highway. *Environ Sci Technol* 40:2531–6.
- Zidek J, Wong H, Le N, and Burnett R. 1996. Causality, measurement error and multicollinearity in epidemiology. *Environmetrics* 7:441–51.

Zielinska B, Sagebiel J, Arnott WP, Rogers CF, Kelly KE, Wagner DA, Lightly JS, Sarofim AF, and Palmer G. 2004. Phase and size distributions of polycyclic aromatic hydrocarbons in diesel and gasoline vehicle emissions. *Environ Sci Technol* 38:2557–67.

Zmirou D, Gauvin S, Pin I, Momas I, Just J, Sahraoui F, Le Moullec Y, Bremont F, Cassadou S, Albertini M, Lauvergne N, Chiron M, and Labbe A. 2002. Five epidemiological studies on transport and asthma: objectives, design and descriptive results. *J Expo Analysis Environ Epidemiol* 12:186–96.

Zmirou D, Masclat P, Boudet C, Dor F, and Dechenaux J. 2000. Personal exposure to atmospheric polycyclic aromatic hydrocarbons in a general adult population and lung cancer risk assessment. *J Occup Environ Med* 42:121–6.

15 Health Effects of Ground-level Ozone

15.1 Exposure Assessment

Ozone concentration measured at ambient central site monitoring stations is the most common surrogate for exposure employed in epidemiological studies. Even though the primary source of exposure to ozone is the ambient air, population and individual exposures can deviate from the levels measured by a central site monitor as a consequence of a variety of factors.

This section discusses information on human exposure to ambient ozone air pollution. It first summarizes information on the levels and patterns in ambient ozone, and then discusses the relationship between the concentrations of ambient ozone and ozone in indoor environments, where most people spend the majority of their time, and on determinants of this relationship. The results of studies of personal exposure to ozone are provided next, including the relationship between ambient ozone and personal exposure to ozone and the factors that modify this relationship. Finally, a summary and considerations with respect to ozone exposure are presented.

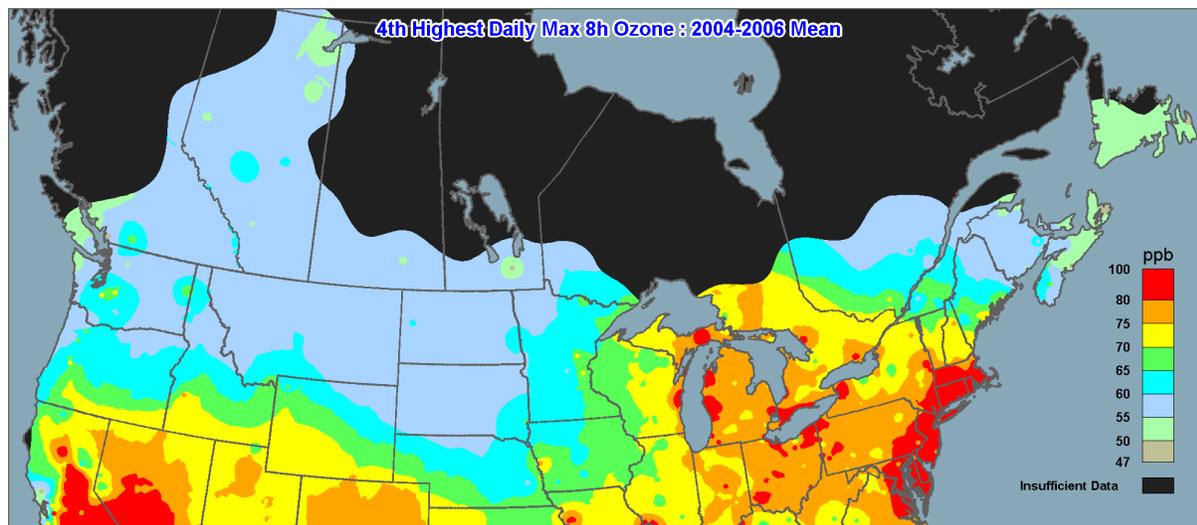
15.1.1 Ambient Ozone: Levels and Patterns

Most people are exposed to ozone principally of ambient origin. Information and data from ambient monitoring of ozone in Canada are discussed in detail in Chapter 3 (Ambient Measurements and Observations) of the companion volume of this assessment, written by Environment Canada scientists (Environment Canada, 2011). This subsection contains a brief summary of the information on ambient levels of ozone contained in that chapter, supplemented with some information from the US EPA 2006 Ozone AQCD, with a focus on those aspects that are most relevant to human exposure to ozone of ambient origin. This is followed by accounts of some more recent studies in this area. Readers requiring more detail are referred to the chapter by Environment Canada.

Most of the ambient ozone measurement data in Canada are generated through two monitoring networks, NAPS and the Canadian Air and Precipitation Monitoring Network (CAPMoN). The NAPS network is run cooperatively by the federal, provincial, territorial and some regional governments that measure air quality throughout Canada, while the CAPMoN program is operated by Environment Canada. Most NAPS sites are located in urban, suburban and industrial areas, whereas CAPMoN sites are in rural and remote locations. In 2006, there were 213 ozone monitoring sites reporting data, including 14 CAPMoN sites.

Daily maximum 8-h ozone concentrations for active stations across Canada for May to September 2004–06 are presented in Figure 15.1, taken from Chapter 3 of this assessment (Canada, 2011). The data reveal that 8-h values over 65 ppb (the CWS value) are limited principally to sites in southern Ontario and Quebec. These areas represent the northern edge of a high-ozone region that includes most of the northeastern US. The lowest concentrations are found in the Yukon, the Northwest Territories, eastern Nova Scotia, and Newfoundland and Labrador. As has been shown previously, mean and median ozone levels are highest at rural sites and lowest at downtown urban sites (where concentrations are reduced as a result of titration by NO emitted from motor vehicles).

Figure 15.1 Spatial distribution of the 3-year-average fourth highest daily maximum 8-h ozone concentration in ppb (2004–2006)

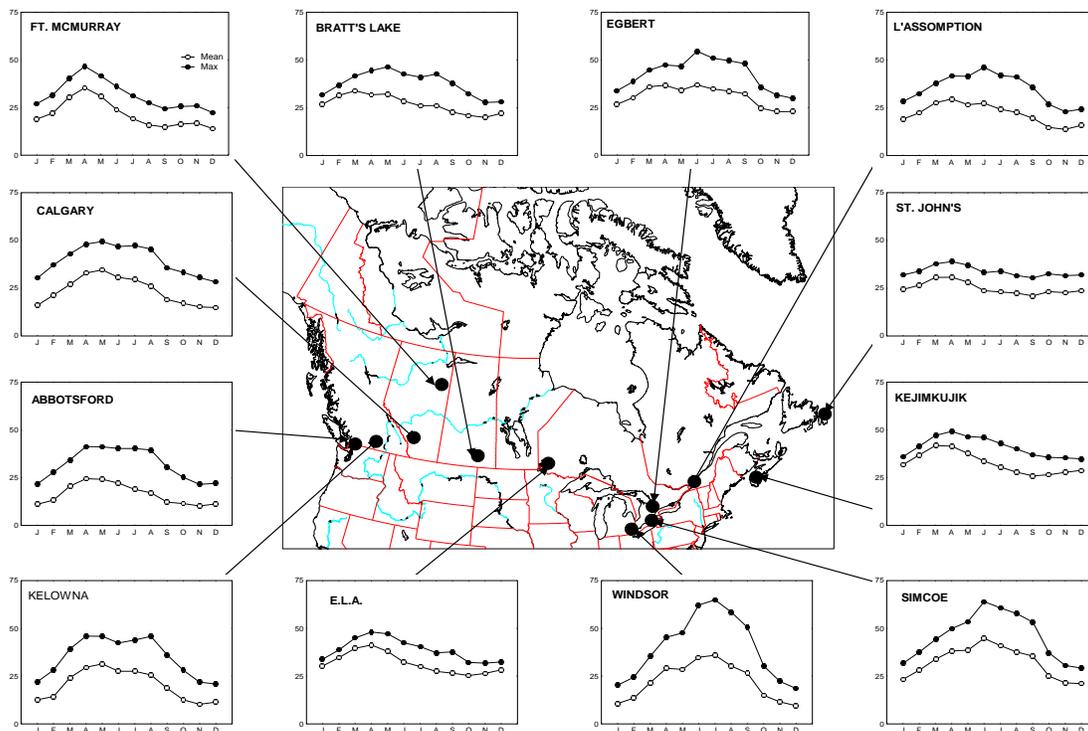


There are pronounced seasonal variations in ozone concentrations throughout Canada, and these differ by region (Figure 15.2 (Canada, 2011)). In southern Ontario and Quebec, many sites experience the highest mean daily maximum ozone levels in the months of June, July or August. In these areas, photochemical ozone formation and LRT of pollutants can contribute substantially to elevated ozone concentrations measured during these months, and summertime maxima are generally higher than levels measured over this period elsewhere in the country. In other regions of Canada, sites typically experience maxima in springtime, with March to May peaks observed, the result of inflow of background ozone and intrusions of stratospheric ozone.

There are substantial diurnal variations in ozone concentrations. Ozone levels tend to peak in early to mid-afternoon in regions where there is strong photochemical production, and later in the day where transport is more important, while nighttime concentrations are much lower (Figure 15.3 (Canada, 2011)). There are large seasonal differences in the amplitude of diurnal variations in ozone; levels in winter remain low and exhibit smaller diurnal variation than in summer. Sites in southern Ontario and Vancouver show the greatest divergence between summer and winter profiles (Figure 15.3 (Canada, 2011)). There are also substantial differences between weekdays and weekends in urban diurnal ozone profiles, with daytime ozone levels being increased on weekends compared with weekdays at most urban sites in the Canadian network (Figure 15.4 (Canada, 2011)). This “weekend effect” is primarily the result of reduced NO concentrations (due to lower traffic volumes, particularly diesel truck traffic) and hence less titration of ozone.

Figure 15.2 Mean and mean daily maximum ozone (ppb) by month averaged for the years 2001 to 2005

(Note: mean ozone concentration in ppb shown on y-axis)

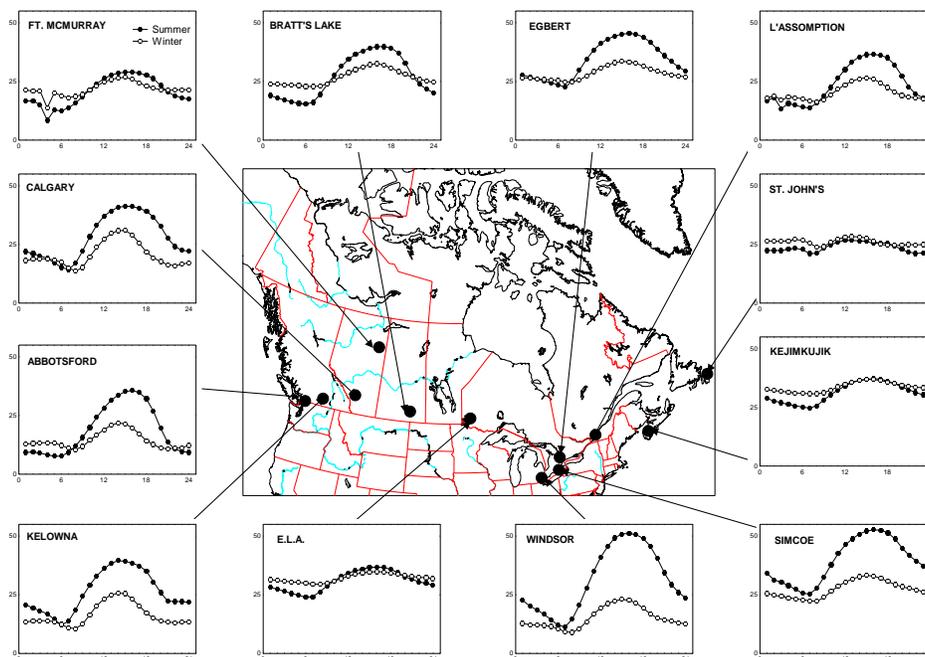


As discussed in the US EPA 2006 Ozone AQCD, though ozone concentrations are generally well correlated across monitoring sites within a given area, there is often considerable spatial variation. As mentioned above, ozone concentrations downtown are often lower than those outside of the city centre, because of titration of NO emitted by motor vehicles. Much higher levels of ozone are often observed downwind of urban centres, the result of photochemical reaction of precursor gases carried from the urban centre. The concentrations of ozone are again decreased in areas that are more remote from precursor sources. Surface-level ozone can also be depleted close to sources of NO, such as roadways and power plants. Ozone near the surface also reacts with surfaces such as buildings and vegetation and with NO emitted by motor vehicles or soil, giving rise to a vertical gradient of ozone that is directed downward and most pronounced during stable conditions. The US EPA concluded that urban centres with low traffic densities located downwind of major sources of ozone precursors are heavily influenced by LRT and tend to show smaller spatial variability than those source area cities with dense traffic located upwind.

Several more recent studies of levels and patterns of ambient ozone were identified and are summarized below. These studies confirm that ambient ozone concentrations fluctuate on diurnal, day-of-week, and seasonal scales, and that ambient ozone is generally more spatially homogeneous than primary pollutants, though titration by NO from vehicle exhaust can markedly reduce ozone levels in the vicinity of major roadways.

Figure 15.3 Diurnal variations in ozone concentration (ppb)—summer (May–Sep) and winter (Nov–Mar) averaged for years 2001 to 2005

(Note: Mean ozone concentration in ppb shown on y-axis)

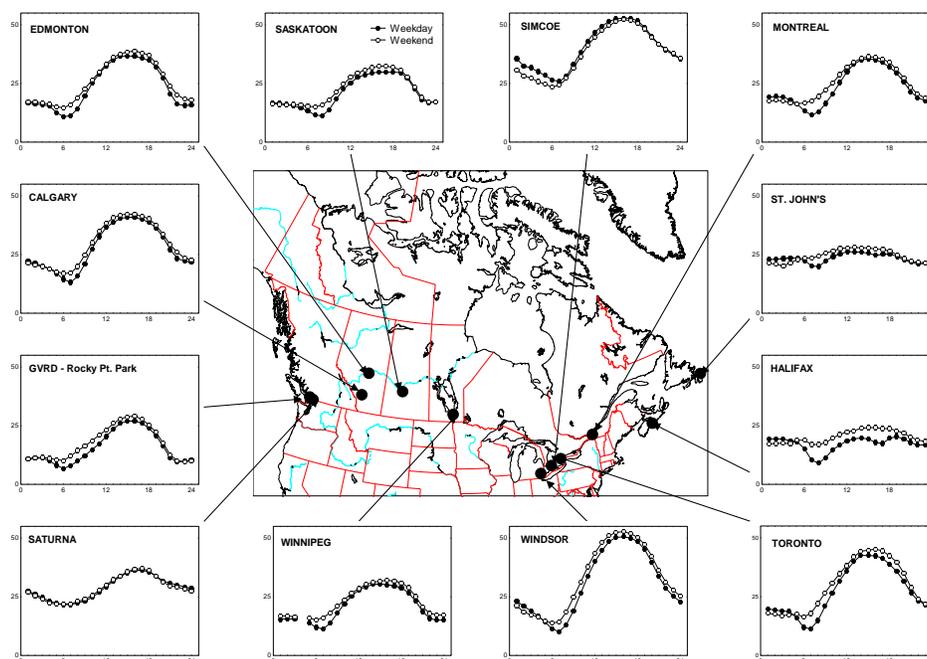


Ito et al. (2005a) investigated monitor-to-monitor temporal correlation of air pollution in the contiguous US between 1988 and 1997. Correlation coefficients between all pairs of monitors within an Air Quality Control Region (AQCR) were relatively high when separation distances were less than 10 mi, with a best estimate of approximately 0.8. The fitted curve declined with increasing separation distance; the estimated correlation coefficient was just under 0.6 at 100 mi, after which the rate of decline was much less. In GAMs with strict convergence criteria, the median correlation coefficient in each AQCR was most strongly related to region (higher in the eastern regions than in the west) and separation distance, rather than to site characteristics like land use or urbanicity. Results were generally similar for PM₁₀ and NO₂, while the primary pollutants CO and SO₂ displayed, on average, lower monitor-to-monitor correlation.

Wade et al. (2006) investigated the error associated with instrument imprecision and spatial variability in the assessment of temporal variation of ambient air pollution in Atlanta, GA, during the 1999–2002 ozone seasons. Using modified semivariograms constructed from the data of three pollution monitoring networks, they estimated that for daily 8-h maximum ozone, instrument imprecision was around 10% and the measure of spatial variability and instrument precision combined was around 30% of the temporal variation. Population-weighted variation in ozone concentrations due to both instrument imprecision and spatial variability was 20% of the temporal variation. All these values were much greater for primary particulate and other gaseous pollutants. Ozone concentrations were very similar across stations, and highly correlated (*r* values for the correlation of various stations with the reference station ranged from 0.98 to 0.85 and decreased with increasing distance). Wind rose plots indicated that ozone levels were not strongly affected by local sources (as expected for a secondary pollutant), except that ozone minima were associated with NO_x peaks, which were in turn associated with vehicle facilities and major roadways.

Figure 15.4 Diurnal variations in ozone concentration (ppb)—weekday and weekend for summertime (May–September) averaged for years 2001 to 2005

(Note: mean ozone concentration in ppb shown on y-axis)



Jo and Park (2005) reported the results of analyses of 5–6 years of data on the concentrations of ozone and other gaseous pollutants at two roadside monitoring sites and one residential location in Daegu, South Korea. Ozone levels were generally higher at the residential site than those measured immediately adjacent to each of two major roadways, probably the result of titration of ozone by NO emitted from motor vehicles. One-hour average concentrations of ozone displayed typical diurnal, day-of-week, and seasonal patterns, including a strong mid-afternoon peak in all four seasons, a slight increase on Sunday, and a marked springtime maximum, respectively. Annual trends differed between the stations; there were significant increases in the 1-h average concentrations of ozone at the residential and one roadside site, and a significant decrease at the second roadside site. Regression equations relating ozone levels at each site to meteorological variables (most often solar radiation, wind speed, and air temperature) were highly significant, with most R^2 values falling between 0.25 and 0.4.

Air quality modelling systems have the potential to alleviate some of the limitations of monitoring networks. Bell (2006) reported the results of a case study in which a variety of ambient exposure estimates were developed for a high ozone episode in the North Georgia region of the US. The estimates were developed using multiple methods for different geographic scales, based on either ambient measurements at eight regional ozone monitors or concentration estimates from a modelling system that combined the Penn State/National Center for Atmospheric Research 5th generation Mesoscale Model (MM5) version 3-4 and the US EPA's Models-3 Community Multi-Scale Air Quality (CMAQ) system. The modelled hourly ozone concentrations closely reproduced the magnitude and timing of diurnal fluctuations over 3 days measured in the 4-km by 4-km grid cell where the monitor was located. The modelled estimates at this scale predicted considerable spatial heterogeneity in ambient ozone concentrations, which was not evident based on the measured monitoring data from the sparse network. For example, in one county, the difference between the lowest and highest maximum hourly ozone

concentrations was 53 ppb for the modelling system and 12 ppb for the nearest monitor approach. However, the authors did not indicate whether the results at sites with markedly different predicted concentrations still tracked one another over time, which is most relevant to the time-series epidemiology studies. The authors noted that although ambient modelling potentially provides better estimates of exposure than monitoring alone, these models require extensive validation and do not consider personal exposure.

NO in vehicle exhaust is known to scavenge ambient ozone. McConnell et al. (2006) investigated the local variation in ambient ozone resulting from variation in traffic patterns near the homes of 78 children who participated in the California CHS. Ambient ozone was measured for 24 h at a central monitor (typically located within a few kilometres of study homes) and outside each home on two occasions in 1994. Ozone concentrations were similar at the homes and the central monitor on average, and were highly correlated, though the residential levels were much more variable in one of the three communities. Measured home ozone concentrations declined in relation to residential NO_x, with the range of NO_x modelled from local traffic using a line source dispersion model accounting for an almost 17 ppb decrease in ozone concentrations. Most of this was due to a small proportion of homes near heavy traffic corridors. These results suggest that residential outdoor ozone levels can be over- or underestimated by measurements at a central monitor, depending on the local distribution of traffic in the community.

15.1.2 Indoor Environments—Levels and Determinants of Ozone

This section initially summarizes the findings of the SAD and US EPA assessments with respect to the levels of ozone in indoor environments, where most people spend the majority of their time. This is followed by a review of the identified studies that were published after the US EPA assessment but still during the period covered by this assessment (i.e. 2005 and 2006).

The 1999 Ozone SAD noted that there are few indoor sources of ozone, and that ozone that infiltrates into buildings is removed by reaction with indoor surfaces. As a result, indoor concentrations of ozone were usually less than ambient concentrations in the available studies, though they were correlated with the ambient levels and tracked the typical diurnal fluctuations in ambient ozone. Most I/O ratios reported were in the 0.5–0.8 range, were generally similar between residential and public buildings, and were highest in indoor microenvironments with high AERs and high ambient ozone levels.

At the time of the US EPA 2006 Ozone AQCD, the number of studies of indoor levels of ozone had increased several-fold. A summary of the findings of the US and Canadian studies reviewed in the US EPA assessment is contained in Table 15.1. This has been modified from a table in the US EPA document and updated to include the results of some more recent studies.

The US EPA 2006 Ozone AQCD noted that the few indoor sources of ozone include photocopiers, fax machines, laser printers, and electrostatic air cleaners and precipitators, which generally have low emissions of ozone. (Ozone generators, sold as home air cleaners, can emit hazardous quantities of ozone. However, these devices are no longer approved by the CSA for use in homes, and Health Canada and other government agencies have issued warnings recommending against their use.) Due to the lack of specific indoor sources, ozone indoors is generally derived from infiltration of ambient ozone from outdoors.

Table 15.1 US and Canadian studies of ozone levels (ppb) and determinants in indoor environments (modified from US EPA, 2006)

Location and ventilation conditions	Indoor/outdoor concentrations Mean (range)	Indoor/outdoor ratios Mean \pm SD	Comments	Reference
<p>Toronto, ON, homes</p> <p>Winter— weekly Summer— weekly</p> <p>Summer— 12 h/day — 12 h/night</p>	<p>1.6 (ND–29.4)/15.4 (0.4–31.4)</p> <p>-/-</p> <p>7.1 (ND–149)/19.1 (ND–54.7)</p> <p>6.2 (ND–66.1)/9.4 (ND–77.8)</p>	<p>0.07 \pm 0.10</p> <p>0.40 \pm 0.29</p> <p>0.30 \pm 0.32</p> <p>0.43 \pm 0.54</p>	<p>Electrostatic air cleaners were present in about 50% of the homes. Air conditioners were present in about 80% of the homes; most were central units that used recycled air. Air conditioners were used in only 13 of the 40 homes on a daily basis. Measurements were made both inside and outside the homes for five consecutive 24-h periods. Homes with electrostatic air cleaners had higher I/O ratios during the winter months. The mean average weekly AER for all homes during the winter months was $0.69 \pm 0.88 \text{ h}^{-1}$ and 50% of the homes had an AER of less than 0.41 h^{-1}. For the summer months, the mean average AER was $1.04 \pm 1.28 \text{ h}^{-1}$ and 50% of the homes had an AER of less than 0.52 h^{-1}. In summer, home outdoor O_3 concentration (C_o) was correlated with indoor O_3 level C_i (correlation not given), while weekly AER was marginally correlated with weekly I/O ratios ($r = 0.36$, $p = 0.05$). During winter C_o, AER, volume of home, energy-saving measures, and house age were not related to C_i or I/O ratios. Weekly home outdoor O_3 levels strongly correlated with closest Ontario Ministry of Environment site measurements: $r = 0.78$ in winter and $r = 0.79$ in summer daytime. (Personal monitoring results in Table 15.2).</p>	<p>Liu et al. (1995)</p>
<p>Boston, MA, homes</p> <p>Winter—continuously 24 h Summer—continuously 24 h</p>	<p>4.2 (ND–20.4)/15.9 (4.4–24.5)</p> <p>6.73 (ND–34.2)/26.34 (8.2–51.8)</p>	<p>0.30 \pm 0.42</p> <p>0.22 \pm 0.25</p>	<p>Study examined the potential for O_3 to react with VOCs to form acid aerosols. Carbonyls were formed. No clear trend of indoor O_3 with AERs. The average AER was 0.9 h^{-1} in winter and 2.6 h^{-1} in summer. Four residences in winter and nine in summer with 24-h average concentrations. Indoor O_3 concentrations were dependent on the outdoor concentrations and AER.</p>	<p>Reiss et al. (1995)</p>
<p>Los Angeles, CA</p> <p>Homes</p> <p>Other locations</p> <p>In vehicle</p>		<p>0.28</p> <p>0.18</p> <p>0.21</p>	<p>Study conducted in September. Monitored O_3 concentrations consisted of twenty-one 24-h periods beginning at 7 p.m. and ending at 7 p.m. on the following day. Ozone concentrations were higher at the fixed monitoring sites during the afternoon. The weather was sunny and the temperature was high. I/O ratio was lower when windows were closed. The effect of A/C on the I/O varied. PEM O_3 levels tended to be higher when O_3 concentration at the nearest fixed-site monitor was high.</p>	<p>Johnson (1997)</p>

Location and ventilation conditions	Indoor/outdoor concentrations Mean (range)	Indoor/outdoor ratios Mean \pm SD	Comments	Reference
Los Angeles, CA, homes Summer Winter	13 (<5–73)/37 (<5–108)	0.37 \pm 0.25 0.43 \pm 0.29 0.32 \pm 0.21	From February to December, 481 samples were collected inside and immediately outside of the homes. Ratios were based on 24-h average O ₃ concentrations indoors and outdoors. Low outdoor concentrations resulted in low indoor concentrations. However, high outdoor concentrations resulted in a range of indoor concentrations and ratios. I/O ratios were highest during the summer pollution months. Moderate to strong correlations were observed between indoor O ₃ levels and O ₃ levels at the monitoring station (r = 0.49), between O ₃ levels at the monitoring station and O ₃ levels outside the house (0.76), and between indoor O ₃ levels and O ₃ levels outside the house (0.58).	Avol et al. (1998a, 1998b)
Upland and Lake Arrowhead, CA, homes Arrowhead, no AC, windows open Upland AC, windows closed Gas stove off, windows open Gas stove on, windows open		0.68 0.09 0.82 0.15	I/O ratio was determined for 20 homes. Only three of the homes operated the air conditioning. I/O ratios were based on 24-h continuous ambient concentrations and 0.5–1 h average indoor concentrations. In one home, the indoor O ₃ concentrations were considerably reduced within 7 min when the gas stove was on.	Lee et al. (1999)
Southern CA homes Upland Mountain towns Overall, A/C Overall, no A/C Ozone season Upland Mountain towns Non-ozone season Upland Mountain towns Ozone season Female children Male children Non-ozone season Female children Male children	 11.8/48.2 21.4/60.1 3.2/21.1 2.8/35.7 16.8/54.5 16.1/54.0 2.9/28.8 3.1/27.8	0.28 \pm 0.19 0.19 \pm 0.16 0.26 \pm 0.18 0.20 \pm 0.17 0.31 ^a 0.30 ^a 0.10 ^a 0.11 ^a	Ozone measurements were taken at 119 homes (57 in Upland and 62 in towns located in the mountains) over 6 consecutive day sampling periods (~144 h) per month, for 12 months (I/O ratios are from April and May only). I/O ratios were based on average monthly outdoor concentrations and average weekly indoor concentrations. The I/O ratio was associated with the home location, number of bedrooms, and the presence of an air conditioner. I/O ratios are based on a subset of the homes. Measurements inside and outside 156 homes with 224 children over 6 consecutive day sampling period (~144 h) per month for at least 6 of the 12 months. Ozone levels at central monitor were similar to those outside of each home, though less variable. Concentrations were highest in the O ₃ season and in outdoor samples, markedly lower in the non-O ₃ season and in indoor and personal samples. Ozone levels indoors and outdoors were not significantly different between boys and girls, though personal levels were higher in boys in both seasons. (Personal monitoring results in Table 15.2).	Lee et al. (2002); Geyh et al. (2000) Xue et al. (2005)

Location and ventilation conditions	Indoor/outdoor concentrations Mean (range)	Indoor/outdoor ratios Mean \pm SD	Comments	Reference
Nashville, TN, homes Grand mean	2.05 (ND–17.9)/21.12 (11.2–35.6)	0.1 \pm 0.18	Week-long average outdoor, indoor and personal O ₃ exposures of 36 children were measured weekly for 6 weeks during June and July using passive samplers. Levels measured outdoors correlated well with those at central monitoring sites. Indoor levels were significantly lower for houses with central A/C, those that did not use window fans, and those that did not open windows. (Personal monitoring results appear in Table 15.2.)	Lee et al. (2004)
Southern California Museum Buffer zone—roll-up door closed Buffer zone—roll-up door open Trail View Window (exhibit)	7.05/22.17 24.33/28.2 3.1/9.43	0.27 \pm 0.15 0.88 \pm 0.15 0.33 \pm 0.15	Measurements made over a 2-week period (24-h average). I/O ratios for the pollutants with outdoor sources such as O ₃ showed substantial variations, from low values at locations without influx of outdoor air to high values at locations experiencing high influx of outdoor air.	Hisham and Grosjean (1991)
Burbank, CA Telephone switching station	0.2–8/1.0–21.1 (medians)	0.12–1.09 ^a (medians)	Continuous sampling for 14 months. Major source of O ₃ was transport from outdoors. Indoor O ₃ concentrations closely tracked outdoor concentrations, measuring from 30% to 70% of the levels outdoors. From early spring to late fall O ₃ concentrations peaked during the early afternoon and approached zero at sunset. AER ranged from 1.0 to 1.9 h ⁻¹ .	Weschler et al. (1994)
Raleigh, NC Patrol cars	11.7/28.3	0.41 ^a	Patrol cars were monitored Monday through Thursday between 3 p.m. and midnight on 25 occasions during the months of August, September and October. Outdoor O ₃ concentrations were taken from ambient monitoring station. Air inside the patrol car was recirculated cool air. Ozone concentrations in the car were found to closely follow those outdoors.	Riediker et al. (2003)

^a Value calculated from the data in the original report of the study

The US EPA 2006 Ozone AQCD also reported that levels of ozone in indoor environments depend primarily on several factors, including the concentration of ozone outdoors, outdoor/indoor infiltration, the AER, and removal by chemical reaction. Therefore, indoor ozone concentrations tend to reflect those outdoors and are greater when ozone levels outdoors are greater, often tracking the diurnal, day-to-day and seasonal variations in outdoor ozone. AERs vary as a result of indoor–outdoor temperature differences, wind effects, geographical region, type of heating/ventilation system, and building type and vintage. Because ozone that infiltrates indoors reacts with surfaces and other contaminants, concentrations are typically lower indoors than outdoors. Buildings with greater surface area/volume ratios, as for smaller rooms and those with fleecy materials/furnishings or with high indoor air levels of unsaturated VOCs (primarily terpenes or related compounds) or NO from gas stoves, will remove ozone more rapidly.

Reflecting the influence of these factors, studies of indoor levels of ozone in various residential and public buildings reviewed in the US EPA 2006 Ozone AQCD revealed that indoor ozone concentrations typically vary across all such locations. The levels were also generally greater with higher AERs and in the ozone season, while still lower than outdoor ozone levels (Table 15.1). Additional factors that affected indoor air levels of ozone were the use of A/C (reduced levels), window fans (increased them), and window opening (increased them), each of which affects AERs and hence infiltration rates and residence times (Table 15.1). In vehicles, as in other enclosed environments, ozone concentrations increased with increasing air mixing and sometimes approached levels outdoors if the windows were kept open.

Two recent studies (not reviewed in the US EPA 2006 Ozone AQCD) were identified in which indoor levels of ozone in public buildings were investigated in relation to ambient levels. The results of these studies confirm the dependence of indoor ozone concentrations on the levels outdoors and on building air exchange.

Blondeau et al. (2005) and Poupard et al. (2005) investigated the ozone levels at eight schools in La Rochelle, France, and its suburbs. Ozone was monitored continuously indoors and outdoors at each school for two 2-week periods, one in winter and one in spring/summer. Indoor concentrations of ozone were less than those outdoors; the mean I/O ratio ranged from 0 to 0.45 for different schools and seasons. The more airtight the building the lower the I/O ratio was, and opening windows significantly increased the ratio. There were no consistent differences between spring/summer vs. winter I/O ratios. The I/O ratio was negatively correlated with outdoor ozone in the most airtight buildings, perhaps because there was more efficient ozone scavenging as a result of increased residence times indoors, but the ratio generally increased with increasing outdoor ozone in less airtight buildings. Indoor ozone concentrations remained close to zero in the most airtight school, even in the face of strong outdoor variations, but tracked short-term fluctuations in the outdoor concentrations in the least airtight building. Mean outdoor concentrations of ozone ranged from 15 to 41 ppb, and maxima from 41 to 66 ppb; peak values were generally greater in spring/summer than winter, whereas the pattern was less clear for the average levels. The authors concluded that building airtightness and outdoor concentrations strongly influence the I/O concentration ratios for ozone.

Loupa et al. (2006) studied ozone levels in two medieval churches in Cyprus, one located in an urban area and the other in a rural area. Indoor concentrations of ozone tracked the diurnal fluctuations in outdoor ozone at both churches during winter and summer sampling periods of several days. I/O ratios of ozone concentrations in the summer were near to unity for both churches, due to enhanced AER from open windows. During winter, I/O ratios fell to less than half their summer values, due to reduced AER, and were lowest (0.16 to 0.36) in the one church where the burning of candles (a source of NO, which can scavenge ozone) was practised.

Two recent studies were identified in which ozone emissions from indoor sources, including office equipment and electronic air cleaners, were investigated.

Black (2006) measured emissions of a variety of compounds including ozone during the operation of dry process photocopiers, laser printers, and personal computers. The experiments were conducted in dynamic environmental chambers designed to simulate normal room conditions with respect to such features as temperature, relative humidity, and ventilation. Dry process photocopiers were reported to have the highest emissions of ozone (mean 4.2 mg/h, range 1.2–6.3 mg/h), followed by laser printers (mean 0.8 mg/h, range <0.02–6.5 mg/h), while personal computers did not emit measurable quantities of ozone (<0.02 mg/h). It was estimated that average exposure concentrations resulting from these emissions over an 8-h day in a typical office would be 0.04 mg/m³ (20 ppb), 0.01 mg/m³ (5 ppb) and <0.001 mg/m³ (<0.5 ppb) respectively.

Some air cleaners are known to generate ozone. Chen et al. (2005) used a full-scale dynamic chamber to test 15 air cleaner systems for their initial VOC removal efficiencies and generation of ozone. Air cleaners that employed ozone oxidation or air ionization generated high chamber concentrations of ozone, some in excess of 100 ppb, and the only VOC they removed was d-limonene, which contains unsaturated carbon-carbon bonds and can therefore react with ozone more quickly than other VOCs. Lesser quantities of ozone were emitted from individual sorption filtration units due to the use of an electronic cell or a plasma unit. Ozone generation from the remaining air cleaners was negligible.

15.1.3 Personal Exposure to Ozone

This section initially summarizes the findings of the 1999 Ozone SAD and US EPA 2006 Ozone AQCD assessments with respect to personal exposure of individuals to ozone. This is followed by a review of the identified personal exposure studies that were published after the US EPA assessment, but still during the period covered by this assessment (2005 and 2006).

The 1999 Ozone SAD reviewed a small number of Canadian and US studies of personal exposure to ozone published in the first half of the 1990s. In these studies, personal exposures to ozone were related to the time that people spent indoors vs. outdoors exposed to relatively low and relatively high ozone levels, respectively. As a result, personal ozone concentrations reported were, on average, roughly 70% higher than those in indoor air and 50% lower than those in outdoor air. Although in these studies individual personal exposures to ozone varied greatly between subjects, mean personal exposures to ozone were correlated with those measured at central monitoring sites, suggesting that ozone data from fixed ambient monitors can adequately represent population exposures.

By the time the US EPA 2006 Ozone AQCD was issued, many more studies of personal exposure to ozone had been completed. A summary of the findings of the US and Canadian studies reviewed in the US EPA assessment is contained in Table 15.2, which has been modified and updated from the table in the US EPA document.

In the personal exposure studies reviewed in the US EPA 2006 Ozone AQCD, there was considerable interindividual variability in exposures, as a consequence of differences in activities, housing characteristics, etc. (Table 15.2). In spite of this variability, personal exposures were distinctly lower than ambient concentrations measured at stationary sites, reflecting the large amount of time people spend exposed to lesser concentrations of ozone in indoor environments (in one study in Boston, MA, ambient levels were related to personal levels, but based on the regression between the two variables, were 3- to 4-fold greater in the summer and 25-fold greater in the winter (Sarnat et al. 2005)). In addition, there was a

moderate to strong correlation and/or a significant regression between ozone levels at central sites and personal exposures to ozone in virtually all of the studies; this was often most pronounced in the warm season (Table 15.2).

Outdoor workers and children had somewhat greater personal exposures to ozone than other groups and these tended to be more strongly correlated to ambient ozone levels, reflecting their longer time spent outdoors and their increased activity (Brauer and Brook, 1997; Lee et al., 2004; Sarnat et al., 2005). Boys also spent more time outdoors and had higher personal exposure to ozone than girls in a California study (Geyh et al. 2000). In another study from California mentioned in the US EPA assessment, there was a significant reduction in children's hospital admissions for asthma on smog alert days, indicating that avoidance behaviour can modify exposure and the association between health effects and air pollution. The US EPA 2006 AQCD concluded that, although ozone concentrations measured at stationary ambient monitoring sites may not explain the variance in individual personal exposures, they are likely to be representative of the day-to-day changes in ozone exposure experienced by the population, and appear to serve reasonably well as surrogate measures for aggregate personal exposures (i.e. exposure at a population level).

A small number of more recent studies of personal exposure to ozone, all of them conducted in the US, were identified. The design and results of the individual studies are summarized below, and have also been used to update Table 15.2.

Sarnat et al. (2005) reported the results of a personal exposure study conducted in Boston, MA, during the summer of 1999 and the winter of 2000. (Though some of the results of this study were reported in the US EPA 2006 Ozone AQCD, the study is reviewed here because the US EPA review only presented a limited subset of the findings. As well, additional details of the results were presented in the later Health Effects Institute report of this study (Koutrakis et al., 2005).) Personal exposures to ozone were measured for 24 h/d for 12 consecutive days, on cohorts of 20 healthy seniors and 23 children 9–13 years of age, for a total of 714 person-days of exposure to ozone and other pollutants. All subjects were non-smokers and lived in non-smoking residences. Personal ozone exposures for both seniors and children were generally lower than concentrations of ozone at local stationary ambient monitoring sites and frequently lower than their respective detection limits in all sampling periods; these patterns were more pronounced in the winter than in the summer (Table 15.2). In mixed model regressions relating personal exposures to ambient concentrations, the slope was significant in both seasons and was greater in the summer than in the winter (slope in summer 0.27 (95% CI 0.18–0.37) and in winter 0.04 (95% CI 0.0–0.07)). Eight subjects of 29 had individual personal–ambient ozone correlations greater than 0.8 during the summer. With respect to other pollutants, personal–ambient regressions had greater and more significant slopes for both $PM_{2.5}$ and SO_4^{2-} during both the winter and summer sampling periods, while for NO_2 the slope for the summer period was significant but less than that for ozone.

These results contrast with an earlier study by the same research group reviewed in the US EPA 2006 AQCD, in which personal exposures to ozone in 56 subjects (including healthy seniors, children, and COPD patients) in Baltimore, MD, during 1998 and 1999 were not related to ambient ozone in either winter or summer (slope in winter 0.01 (95% CI -0.01–0.03) and in summer 0.03 (95% CI -0.02–0.09) (Sarnat et al., 2000; Koutrakis et al., 2005). While no quantitative measures of ventilation were made in either city, Sarnat et al. (2005) suggested it was likely that the average AERs for the relatively older, leakier homes of Boston subjects were greater than those in Baltimore, where many of the subjects lived in apartment complexes with central A/C; the prevalence of A/C among Boston subjects was substantially lower. This

Table 15.2 US and Canadian studies of levels (in ppb) and determinants of personal exposure to ozone (modified from US EPA, 2006)

Location, population, Sample duration	n	Personal exposure Mean \pm SD (range)	Outdoor concentrations ^b Mean \pm SD (range)	Comments	Reference
Toronto ON, homes 34 subjects in winter, 89 in summer (most winter subjects plus family members) winter samples for 1 week summer samples 12-h daytime for 5 d	71	1.3 \pm 2.9 (0-19.6)	11.4 \pm 3.0 (6.9-16.3)	Personal O ₃ exposures differed greatly between subjects, and were comparable to those inside the homes in both seasons, but lower than those outside the home or at a central site, most pronounced in winter. Summertime personal O ₃ exposure were significantly correlated with outdoor concentrations at a central site (r=0.22) and fraction of time spent outdoors (r=0.40). A regression model incorporating microenvironmental O ₃ concentrations and time spent explained 72% of the variance in summertime personal exposures (indoor monitoring results in Table 15.1).	Liu et al. (1995)
	424	8.2 \pm 8.7 (0-52.9)	18.5 \pm 9.6 (5.2-35.1)		
San Diego, CA , daily, asthmatics ages 9–18, 12-h sample (daytime), for up to 6 weeks in Sept/Oct	12	12 \pm 12 (0–84) 10 weekend 12 weekday	43 \pm 17 (14–87)	Mean O ₃ personal levels were lower on Friday through Sunday than during the rest of the week (not accounted for by time spent outdoors); opposite day-of-week trend in the stationary-site outdoor O ₃ measurements. Personal O ₃ exposures differed greatly between subjects, averaging 27% of mean outdoor O ₃ levels. Moderate correlation between 12-h average O ₃ concentration at the outdoor stationary site and personal O ₃ measurements (overall R = 0.45; range: 0.36–0.69 by individual; p < 0.001). Model accounting for O ₃ levels and fraction of time spent indoors and outdoors accounted for 25% of variance in personal exposures.	Delfino et al. (1996)
Vancouver, BC adult workers, 24-h sample for 14 d (Groups 1 & 2) or during outdoor work shift (Group 3) in summer (1) Office workers (2) Staff of an overnight camp (3) Farm workers	25	(ND–9)	(5.5–30)	Mean personal O ₃ exposures and ambient fixed-location O ₃ concentrations were well-correlated: r = 0.60, 0.42 and 0.64 for group 1, 2 and 3, respectively. Groups 1 and 2 showed an association between the differences in personal O ₃ exposure and the fraction of time a person spent outdoors. Mean personal to ambient fixed-location O ₃ ratio increased with increasing mean amount of time spent outdoors within and between groups, being roughly unity for the outdoor farm workers and much lower for Groups 1 and 2.	Brauer and Brook (1997)
	25	(ND–12)	(11–26)		
	15	(2–44)	(8.5–50)		

Location, population, Sample duration	n	Personal exposure Mean ± SD (range)	Outdoor concentrations ^b Mean ± SD (range)	Comments	Reference	
Alpine, Southern California subjects (10–38 yrs), 12-h samples daily for 8 weeks				Outdoor measurements at the Alpine APCD site were significant predictors of personal exposure but only explained small amount of variance ($R^2 = 0.07$; $p < 0.01$ in fall and an $R^2 = 0.04$; $p < 0.01$ in spring). Microenvironmental models using outdoor levels and simple time–activity data improved predictions somewhat ($R^2 = 0.22$ or less). In spring, personal O_3 exposures were highest on Saturday and lowest on Monday and Tuesday, with a similar trend being observed for outdoor O_3 measurements and time spent outdoors.	Liu et al. (1997)	
	Spring	22	13.6 ± 2.5 (ND to 80)			63.1 ± 16.3
	Fall	18	10.5 ± 2.5 (ND to 50)			54.5 ± 12.1
Southern California children (ages 6–12), 24-h samples for 6 consecutive days each month for a year (~144 h/month)	169			In O_3 months, children living in Mountain were outdoors longer and exposed to higher outdoor levels than those in Uplands; personal exposure was higher in Mountain ($p < 0.01$). In non- O_3 months, children spent less time outdoors; there was no significant difference in personal exposure between the two communities ($p > 0.05$). Boys had higher personal exposure than girls independent of location or housing factors, especially in summer when boys spent longer time outdoors than girls. Though there were systematic differences in personal, indoor, home outdoor and stationary site O_3 levels, the monthly averages paralleled one another in both communities.	Geyh et al. (2000)	
		Upland—winter	6.2 ± 5.4 (0.5–41)			21.1 ± 10.7 (0.5–65) (O)
		—summer	19 ± 10.1 (0.5–63)			48.2 ± 12.2 (9–83) (O)
		Mountain—winter	5.7 ± 5.1 (0.5–31)			35.7 ± 9.3 (14–66) (O)
	—summer	25 ± 13.4 (0.5–72)	60.1 ± 17.1 (4–160) (O)			
	160	O_3 season—girls	20.8 ± 11.7	54.5 ± 15.7 (O)	Analyses were restricted to children with data for at least 6 of the 12 months. Levels at the central site monitor were very similar to those outside the houses on average. Several hierarchical mixed models were used to predict exposure. The most important predictors overall were indoor O_3 , central ambient O_3 , outdoor O_3 , season, gender, outdoor time, fan usage, and gas range in house. Model with central ambient O_3 , outdoor time, fuel type, house location and season yielded R^2 of 0.58. (Indoor results appear in Table 15.1).	Xue et al. (2005)
		—boys	23.2 ± 13.4	54.0 ± 17.0 (O)		
Non- O_3 season—girls		5.4 ± 5.0	28.8 ± 12.2 (O)			
—boys	6.8 ± 5.6	27.8 ± 12.8 (O)				

Location, population, Sample duration	n	Personal exposure Mean \pm SD (range)	Outdoor concentrations ^b Mean \pm SD (range)	Comments	Reference
Baltimore, MD technician, hourly ^b , daytime sample only, for 15 d in each season while doing scripted activities Winter Summer	1	3.6 \pm 7.5 (ND–49) 15 \pm 18 (ND–76)	(Estimated from graph) (12–24) (12–59)	Spearman correlation coefficient (r_s) between hourly personal daytime O ₃ exposures and central ambient O ₃ levels in summer and winter respectively was: a) $r_s = 0.09$ ($p > 0.05$) and $r_s = 0.05$ ($p > 0.05$) while indoor residence (A/C highrise), b) $r_s = 0.34$ ($p > 0.05$) and $r_s = 0.46$ ($p < 0.05$) while indoor other, c) $r_s = 0.91$ ($p < 0.05$) and $r_s = 0.77$ ($p < 0.05$) while outdoors near roadway, d) $r_s = 0.68$ ($p < 0.05$) and $r_s = 0.86$ ($p < 0.05$) while outdoors away from road, e) $r_s = 0.72$ ($p < 0.05$) and $r_s = 0.57$ ($p < 0.05$) while in vehicle.	Chang et al. (2000)
Nashville, TN elementary school children (10–12 yrs), 13 h, weekly sample for 6 weeks in summer Grand mean Outdoor time <25% 25–75% >75%	36	3.47 (0.6–25.4) 1.5 \pm 0.74 2.0 \pm 1.6 4.2 \pm 2.6	21.12 (11.2–35.6) (O) 21.41 \pm 1.94 (O) 21.22 \pm 2.06 (O) 21.06 \pm 2.3 (O)	Weekly O ₃ ambient levels from the continuous ambient monitoring stations correlated well with passive samples outside of the subjects' homes (correlation not given). Personal O ₃ exposure was correlated with time spent indoors (Pearson r , of -0.17 ($p < 0.01$)) and time spent outdoors (r of 0.19 ($p < 0.01$)), but not with transit time. Having a pet was associated with higher personal O ₃ exposures for 4 of the 6 weeks, and children with pets tended to spend more time outdoors than children without pets. In mixed regression models, significant predictors of personal exposure were 3 or more hours spent outdoors, presence of a pet, and use of a window fan. (Indoor results appear in Table 15.1).	Lee et al. (2004)
Baltimore, MD 20 healthy seniors (>65 yrs), 21 children (9–13 yrs), 15 individuals with COPD, 24-h samples for 12 d in a row Summer—Seniors —Children Winter—Seniors —Children —COPD	56	3.8 \pm 4.5 2.1 \pm 4.8 -0.1 \pm 3.0 0.4 \pm 2.2 1.1 \pm 2.3	37.6 \pm 7.9 32.9 \pm 11.6 18.1 \pm 10.0 (All)	Personal O ₃ exposures were much lower than levels at local stationary ambient monitoring sites and were frequently below the DL, during each season, especially in winter. Personal–ambient mixed model regression was not significant and very close to zero, with the slope being slightly greater during summer (slope of 0.03; 95% CI -0.02–0 .09) than in winter (slope of 0.01; 95% CI: -0.01–0.03). Many of the subjects lived in apartment complexes with central A/C, and subjects spent an average of only 2.4–2.7% (winter) to 5.5–5.7% (summer) of their time outdoors.	Koutrakis et al. (2005) Sarnat et al. (2000)

Location, population, Sample duration	n	Personal exposure Mean \pm SD (range)	Outdoor concentrations ^b Mean \pm SD (range)	Comments	Reference
Boston, MA 20 healthy seniors (>65 yrs), 23 children (9–13 yrs), 24-h sample for 12 d Summer—Seniors —Children Winter—Seniors —Children	43	5.1 \pm 6.6 7.0 \pm 6.9 1.2 \pm 1.7 1.3 \pm 2.1	22.9 \pm 9.8 27.4 \pm 15.3 16.8 \pm 6.1 (All)	Personal O ₃ exposures were much lower than corresponding central ambient concentrations and frequently lower than their respective DL, during each season, especially in winter. Subjects spent a greater fraction of time outdoors during summer (7.3–11.3%) than in winter (2.1–3.3%) on average. Personal–ambient mixed model regression was stronger in summer (slope of 0.27; 95% CI 0.18–0.37) than in winter (slope of 0.04; 95% CI 0.00–0.07). Median subject-specific ambient–personal Spearman's correlation r _s was approximately 0.6 in summer (from graph).	Koutrakis et al. (2005) Sarnat et al. (2005)
Steubenville, OH senior adults (71.8 yrs), 24-h sample for 8–24 d Summer Fall	10	5.3 \pm 5.2 3.9 \pm 4.4	29.3 \pm 13.4 16.0 \pm 8.1	Slopes of personal–ambient central site regressions were moderate and significant in both seasons: slope = 0.15 \pm 0.02 (\pm SE); R ² = 0.24; (p < 0.05) in summer and slope = 0.27 \pm 0.03 (\pm SE); R ² = 0.25; (p < 0.05) in fall. Personal–ambient O ₃ association was influenced by the home ventilation especially in summer, when the association for subjects spending time in indoor environments with open windows (slope = 0.18 \pm 0.03 (\pm SE); R ² = 0.27) was twice that of individuals spending no time indoors with open windows (slope = 0.08 \pm 0.04 (\pm SE); R ² = 0.19). In fall, the difference was similar but less pronounced.	Sarnat et al. (2006a)

^a ND = not detected

^b Outdoor concentrations reported are those measured at central site monitor(s), except for those marked with (O), which were measured outside of each residence.

suggestion was also supported by the finding of higher mean personal–ambient SO_4^{2-} ratios in Boston than in Baltimore during both seasons. This probable difference in AERs between the two studies could account for the discrepant results. However, subjects in Boston also spent somewhat more time outdoors on average, and hence had higher personal exposures to ozone in both seasons (Table 14.5.2). In addition, a large majority of personal ozone levels were less than the LOD for both cities and both seasons; this was particularly pronounced for winter samples in Baltimore, virtually all of which were below the LOD. The high frequency of values below the LOD makes it impossible to discern whether there were actually strong correlations between ambient and personal levels of ozone.

In a more recent study, Sarnat et al. (2006a) investigated personal exposures to ozone in relation to ambient concentrations in senior adults residing in Steubenville, OH, in the summer and fall of 2000. Ten non-smoking subjects participated in each season, with five of them participating in both seasons. Between 8 and 24 repeated 24-h personal measurements per subject were made in each season, for a total of 194 measurements in the summer and 228 in the fall. The personal–ambient relationship depended on season and ventilation. Personal concentrations and concurrent 24-h ambient concentrations measured at a central monitoring site were greater in summer than in fall, with personal levels averaging roughly 0.2 times the ambient levels in each season (Table 15.2). The slopes and R^2 values for personal–ambient regressions were modest and significant for both seasons (summer slope 0.15 ± 0.02 , R^2 0.24; fall slope 0.27 ± 0.03 , R^2 0.25). The influence of home ventilation was evident in both seasons, and clearest in summer, with the slope for subjects spending time in indoor environments with open windows being roughly twice that of subjects spending all their indoor time with windows closed. Results for other pollutants were similar, though the personal–ambient regressions for particles generally had greater slopes and R^2 values than those for gaseous pollutants, including ozone.

Most of the studies summarized in Table 15.2 examined personal exposures to ozone over periods from 12 to 24 h; i.e. for somewhat longer durations than those with which associations with health effects have been reported. However, this is not considered to diminish the relevance of the exposure research to the health effects literature, since these longer periods would include the ozone peaks, with the result that ozone concentrations over the various periods (i.e. 1, 8 or 24 h) are typically highly correlated.

15.1.4 Summary and Considerations: Exposure Assessment

There are few indoor sources of ozone, and so most people are exposed to ozone principally of ambient origin. This takes place both when people are outdoors and when they are in indoor environments into which ambient ozone has infiltrated.

Ambient ozone levels display marked variations in time and space. Throughout the day, ozone concentrations tend to peak in early to mid-afternoon in regions where there is strong photochemical production and later in the day in locations where transport is more important, while nighttime levels are much lower. Seasonally, many sites in southern Ontario and Quebec exhibit summertime maxima in daily maximum ozone levels, while in other regions the maxima typically occur in the spring. Eight-hour ozone concentrations over 65 ppb (the value for the CWS for ozone) are observed primarily in sites in southern Ontario and Quebec. Ambient levels of ozone in a region are generally more spatially homogeneous than other air pollutants. However, concentrations of ozone are often reduced in downtown areas and/or in the vicinity of roadways by NO in vehicle emissions, or increased in rural areas by photochemical generation of ozone from precursor gases during transport from urban centres.

Ozone indoors is generally the result of infiltration of ozone from outdoors. A number of studies have shown that indoor concentrations of ozone and I/O ratios are generally greatest in the ozone season, when outdoor levels and AERs are highest, though indoor levels are still less than those outdoors as a result of chemical reactions with indoor surfaces and pollutants. For example, in the sole Canadian study identified, the mean I/O ratio over a week was 0.40 in summer, compared with 0.07 in winter, and the summer I/O ratio was marginally correlated with the AER (Table 15.1). The results of the other studies summarized in the table, though limited in number and scope, generally confirm the roles of outdoor ozone and air exchange in determining concentrations of ozone in indoor environments.

Personal exposures to ozone will vary over time and as a person moves among locations. The results of most studies have indicated that personal exposures are typically less than ambient levels and greater than those indoors, and have revealed large differences in exposure between subjects (Table 15.2). However, in spite of these differences, in virtually all the available studies, measured personal exposure to ozone for groups or individuals was moderately to strongly related to ambient concentrations measured at a central monitoring site, yielding correlation coefficients on the order of 0.4–0.6 or modest regression slopes. In most of these studies, personal exposure was related to the time spent outdoors and/or was stronger in summer, when ambient ozone levels, building AERs, and time spent outdoors are generally greater. In several studies increased ventilation was an important modifier of the relationship, by enhancing exposure to outdoor ozone.

Although the correlation is often substantial between ambient concentrations and personal exposure to ozone, the variability in slopes described between seasons and locations could result in different estimated exposures and risks if applied in these various settings. So even though one would expect there to be health effects in different settings, the magnitudes would sometimes differ. The relationship between ambient concentrations and personal exposure to ozone will vary as a result of individual-, city- or region-specific differences in time-activity patterns, indoor air exchange rates, air conditioning, housing conditions, etc., creating potential measurement errors. These errors are expected, based on statistical modelling, to most often reduce effect estimates in the ozone health effects analyses and make it more difficult to detect a true underlying association between the exposure and the health effect under investigation.

Overall, the available findings suggest that, although ozone concentrations measured at a central monitoring station may not explain the individual variance in personal exposure to ozone, they appear to be a reasonable surrogate for exposure at a population level. In addition, though in general personal exposures have been measured to be somewhat less than the corresponding ambient levels, day-to-day variations in concentrations at fixed monitors are likely to be representative of day-to-day changes in ozone exposure experienced by the population. It is these variations over time, rather than the absolute magnitude of the exposure itself, that are the basis for the associations between ambient ozone air pollution and acute health effects reported in the time-series epidemiology studies. (These studies comprise the majority of the evidence linking exposure to ambient ozone to health effects.)

Outdoor workers, children and exercising individuals can be expected to have somewhat greater exposures to ozone than other individuals, because they typically spend more time outdoors and often engage in activities that entail considerable exertion, especially during the warm season when ozone concentrations are greatest. In several of the studies summarized in Table 15.2, personal exposures of outdoor workers or children were increased in relation to time spent outdoors. In addition, the results of epidemiology studies of active adults or children, as well as controlled human exposure studies, indicate that prolonged exposure periods in combination with exertion can magnify the respiratory effects of ozone. Thus, outdoor workers

and others who are active outdoors during the time of day when peak ozone concentrations occur should be considered a vulnerable subgroup for the effects of ozone on respiratory health.

15.2 Dosimetry

Ozone dosimetry refers to the measurement or estimation of the amount of ozone and reaction products reaching and persisting at specific sites in the respiratory tract. Knowledge of ozone dosimetry is necessary for extrapolating experimental results from animals to humans and for better understanding factors that affect the uptake of ozone, such as the effect of changes in breathing conditions, as for example during physical activity.

Ozone dosimetry was not discussed in any detail in the 1999 Ozone SAD, though this report noted that the tissue dose of ozone reaches a maximum in the terminal bronchiolar region in all species. It also emphasized that humans absorb significantly more of a given concentration of airborne ozone than rodents, and that this appears to give rise to an increased response per unit of ambient ozone.

The US EPA 2006 Ozone AQCD briefly summarized the literature on the dosimetry of ozone that had been reviewed in the US EPA 1996 Ozone AQCD and updated this with a detailed examination of new studies published up to the end of 2004.

No more recent (2005–2006) studies of ozone dosimetry were identified. Consequently, this review is based largely on the relevant sections of the US EPA 2006 Ozone AQCD.

15.2.1 Dosimetry of Ozone in the Respiratory Tract

Ozone is absorbed in all three major respiratory tract regions (extrathoracic (ET), tracheobronchial (TB) and alveolar) of laboratory animals and humans. The uptake of ozone in specific regions is determined by the complex interaction of a number of factors. Broadly defined, these factors relate to the structure of the respiratory tract, the nature of the ventilation and the mechanism responsible for gas transport (Miller, 1995). A number of other factors discussed in this section also affect the uptake of ozone within the tract.

There are pronounced differences in the deposition of ozone in various regions of the respiratory tract. In both animals and humans, the efficiency of ozone uptake is greater in the nasal passages than in the oral pathway. During quiet breathing and light-to-moderate exercise when humans are nasal breathers, the conducting airways like the nose could strongly influence regional ozone uptake by removing a large fraction of inhaled ozone from inhaled air before it reaches the pulmonary region (Bush et al., 1996). In fact, the nose may help protect the lower respiratory tract from the effects of ambient ozone by scrubbing ozone from inspired air.

With respect to other regions of the respiratory tract, dosimetric modelling predicts that once ozone gets past the ET region, the tissue dose is low in the trachea, increases to a maximum in the terminal bronchioles and first generation of the pulmonary region, and then decreases rapidly in more distal parts of the pulmonary region. Quantitatively, uptake of ozone by humans at rest is about 80–95%, of which 50% is in the head, 7% in the larynx/trachea, and 43% in the lungs. In the lower respiratory tract, increasing tidal volume increases ozone uptake, whereas increasing flow rate or breathing frequency decreases uptake (US EPA 2006 Ozone AQCD).

Nodelman and Ultman (1999) demonstrated that the uptake distributions of ozone boli in the respiratory tract of adult humans were sensitive to the mode of breathing and to the airflow rate. As flow rates increased, ozone penetrated deeper into the lung; penetration was further increased by oral relative to nasal breathing.

A similar regional shift with increasing ventilation is also predicted by dosimetry models of animals and humans. In most controlled human exposure studies, humans are exposed to ozone while exercising, which allows ozone to penetrate deeper into the lung and increases the potential for damage in the bronchioles and alveoli (US EPA 2006 Ozone AQCD).

The results of a small number of general uptake studies in humans, discussed in the following paragraphs, were summarized in the US EPA 2006 Ozone AQCD. They confirm the influence of ventilation rate, along with some other factors, in determining the uptake efficiency in the respiratory tract. In a study by Rigas et al. (2000), uptake efficiency in both men and women exposed to 0.2 or 0.4 ppm ozone while exercising at a minute ventilation of approximately 20 L/min for 60 min or 40 L/min for 30 min ranged from 56% to 98% and had a statistically significant but weak dependence on concentration, minute ventilation, and exposure time. Intersubject differences had the largest influence on uptake efficiency, resulting in a variation of approximately 10%. Similarly, in a study of ozone uptake in the nasal cavities of men and women exposed to the same concentrations, Santiago et al. (2001) determined that fractional absorption was inversely related to flow rate and concentration, but the effect of each of these was small compared with intersubject variability, which accounted for approximately half of the total variation in fractional absorption.

In the available experimental studies of ozone absorption by humans, men and women were generally similar with respect to the influence of factors such as ventilation rates and volumes, ozone concentration and duration of exposure. However, in one study the uptake fraction with continuous exposure to ozone was significantly greater in men than in women, consistent with the lesser breathing frequency and larger tidal volume in males. In a bolus study described in the same report, total respiratory tract absorption was similar for both sexes, but the findings suggested that in females, the smaller airways and associated larger surface-to-volume ratio caused increased local airway absorption and reduced penetration into the distal lung (Ullmann et al., 2004).

Considering the structural variations of RT and airway dimensions that change from birth to adulthood in animals and humans, it has been suggested that ozone uptake is likely to be age-dependent. In one study, dosimetry modelling of the lower respiratory tract distribution of absorbed ozone in children and adults for quiet breathing estimated similar uptake at both ages (84–88%). Regardless of age and breathing conditions, the largest tissue dose of ozone was predicted to occur in the centriacinar region (CAR), where many animal studies show maximal damage (Overton and Graham, 1989). Another study by Sarangapani et al. (2003) used a physiologically based pharmacokinetic model to predict that total regional extraction was relatively insensitive to age, but that extraction per unit surface area for ozone in the pulmonary region was 2- to 8-fold higher in infants (≤ 1 yr of age) than in adults. Furthermore, the same study showed no significant ozone uptake differences between genders.

Some experimental results have shown that exposure to other pollutants can influence the uptake of ozone. Studies by Asplund et al. (1996) and Rigas et al. (1997) showed that bolus uptake was decreased by prior exposure to ozone and increased by exposure to NO₂ and SO₂. The authors then suggested that with exposure to each of these substances there may be increased production of an ozone-reactive substrate in the ELF due to airway inflammation, and that this substrate is depleted by ozone exposure but not by NO₂ and SO₂.

Understanding dosimetry as it relates to ozone-induced injury is complex, because ozone interacts primarily with the ELF, which contains surfactant and antioxidants. The results of earlier *in vitro* dosimetry studies indicated that uptake efficiency is dependent on chemical reaction. The products of this reaction, which are mainly the result of ozonolysis of polyunsaturated fatty acids and include H₂O₂, aldehydes and hydroperoxides, are mediators of

ozone toxicity. Other products are generated through the reaction of ozone with other ELF constituents. A study by Pryor (1992) indicated that a large fraction of ozone reacts in the liquid lining and that only lung regions with a fluid layer less than 0.1 μ thick (the CAR) will have significant penetration of ozone itself to lung tissue.

15.2.2 Species Homology and Animal-to-human Extrapolation

As noted in the US EPA 2006 Ozone AQCD, there are some important interspecies differences that may affect both the patterns of ozone uptake in the respiratory tract as well as the resulting health outcomes. For example, differences in the branching lung structure (asymmetric vs. monopodial) and the type of breathing (oronasal vs. obligate nasal) between primates and rodents can affect both the regional site and the amount of gaseous uptake. Furthermore, susceptibility to the effects of ozone exposure may be due, in part, to biochemical differences among species. Antioxidant metabolism and other factors, like the cytokine and chemokine responses in animals' defences against ozone exposure, for example, vary widely among species and can influence the effects of ozone. Therefore, integration of interspecies differences regarding ozone dosimetry in the RT is critical in order to extrapolate toxicological results from animal studies to humans.

Both the 1996 and 2006 US EPA AQCDs on ozone reported that the total uptake in the respiratory tract of resting rats is approximately 50% of inhaled ozone as compared with the 80–95% uptake seen in humans.

The switch from nasal to oral breathing as a result of exertion, coupled with increases in respiratory flow, allows ozone to penetrate deeper into the lung, thus increasing the potential for damage to bronchiolar and alveolar tissues (Nodelman and Ultman, 1999). Humans exposed for 2 h to 0.39 mg/m³ radiolabelled ¹⁸ozone during mild exercise (15 min intervals, rest and exercise at 60 L/min ventilation rate) had a 4- to 5-fold higher ¹⁸ozone concentration in BAL than resting rats that were administered ozone under the same concentration and exposure conditions. The humans also showed correspondingly lower effect-levels for BAL inflammatory markers (Hatch et al., 1994). The researchers also noted that ¹⁸ozone was found in the surfactant and soluble protein fractions of the supernatant of human and rat lungs, which confirms that ozone reaches alveolar regions of the lung. As stated in the US EPA 2006 Ozone AQCD, important differences between exercising humans and resting rats that may affect tissue ozone dose include 1) increased ventilation and ozone delivery with increasing exercise; 2) decreased pulmonary ventilation and body temperature in response to ozone exposure in rats; 3) diminished dose received in rats due to burying their noses in their fur during exposure; and 4) high antioxidant concentrations in rat's ELF compared with that of humans, which can convert ozone to inactive products before toxicity occurs.

In spite of structural and ventilatory differences between species, mathematical modelling of ozone deposition in the lower respiratory tract (from the trachea to alveoli) of several animal species and humans shows similar patterns of ozone regional dose, although absolute values differ. The CAR in the lung represents the region with the greatest predicted tissue ozone dose for laboratory animals and humans; despite the rudimentary respiratory bronchioles (monopodial and asymmetric branching system) of the CAR in rats compared with the well-developed CAR in non-human primates (dichotomous and symmetric branching system), both species show similar ozone inflammatory responses in the lung tissue.

For similarly exposed animals (same ozone concentration and exposure duration), intra- and interspecies differences in pulmonary responses are observed as a function of animal age, ventilation, and antioxidant status. Early studies ranked mice > rats > guinea pigs in order of

antioxidant responsiveness to ozone challenge. Although antioxidants seem to have an important role in the conversion of ozone to inactive products, differences in the levels of antioxidants between species and regions of the lung do not appear to be the primary factor determining susceptibility to ozone (Kari et al., 1997; Gunnison and Hatch, 1999; Plopper et al., 1998).

15.2.3 Summary and Considerations: Dosimetry

Ozone is a highly reactive gas that is absorbed in all three major regions of the respiratory tract of experimental animals and humans. Uptake efficiency is chemical-reaction dependent, and reaction products of inhaled ozone with lung ELF are directly responsible for the toxic effects and pulmonary damage. According to many studies, uptake and regional respiratory tract distribution of inhaled ozone is sensitive to the mode of breathing (nasal > oral breathing) and to airflow rate. Ozone uptake efficiency is inversely proportional to flow rates and directly proportional to tidal volume; individuals exposed to the same concentration of ozone vary substantially in the amount of actual dose received, reflecting differences in the size of the airways, different breathing patterns, etc. Bolus-response studies have demonstrated that previous continuous exposure to ozone decreases the absorption of a bolus of ozone, perhaps due to depletion of compounds able to react with ozone, whereas continuous exposure to NO₂ and SO₂ increased absorption of a bolus of ozone. These data are of some relevance to environmental exposures where humans are exposed to variable concentrations of all of these pollutants as mixtures.

In humans, ozone uptake efficiency is between 80 and 95%, of which approximately 7% of inhaled ozone is removed in the larynx/trachea, 50% in the head airways (nose and mouth), and 43% in the lungs (TB and pulmonary). The oral vs. nasal breathing, coupled with increased respiratory flow (as occurs during physical exercise), causes a shift in regional ozone dose deeper into smaller lung airways, thus increasing the potential for bronchiolar and alveolar tissue damage. Studies showed that the highest ozone dose is likely to be found in the CAR of the lung, defining CAR as the primary site of ozone-induced lung damage in many animal species, including humans. Available information indicates that humans absorb significantly more of a given concentration of airborne ozone than rodents and this appears to give rise to an increased response per unit of ambient ozone.

Currently, the small number of studies of ozone dosimetry limits the ability to interrelate findings in animals to humans. Comparisons of acute exposures in animals and humans suggest that both species have similar qualitative responses to ozone exposure, with some interspecies mechanistic disparities that necessitate careful investigation in dose–response relationships. Models incorporating ozone dosimetry and species sensitivity models may permit the quantitative application of data from animals to humans, once they are sufficiently validated. Future studies with laboratory animals exhibiting different ozone sensitivity could help elucidate the complex intra- or interspecies differences in health response following exposure to ozone.

15.3 Animal Toxicology

Experimental animal studies allow the controlled evaluation of responses to ozone exposure under a wide range of concentrations and time frames. Effects on tissue structure and function can be evaluated both during and after exposure by BAL and blood and tissue analysis. One drawback to these studies is the considerable uncertainty involved in quantitatively extrapolating the results of animal inhalation experiments for the purposes of human health risk assessment. The response of an animal model to a single or several well-defined air pollutants does not adequately represent the potential human response to complex pollutant mixtures in the ambient environment. Therefore the results of animal and *in vitro* toxicology studies are best utilized in providing a better understanding of the types of effects resulting from ozone exposure and the possible mechanisms involved. Investigation of ozone health effects using experimental animal models has progressed, and Table 15.3 below presents a qualitative summary of findings of the more recent studies reviewed. Animal studies using high exposure levels (>1 ppm) have been included because they may point to mechanisms that play a role at lower exposure levels. Additionally, these experimental animals have anatomical characteristics that significantly reduce the concentration of ozone reaching the lung in comparison with humans. However, overall it should be emphasized that any interpretation of these studies must bear in the mind that such exposure levels are very high compared with ambient concentrations, leading to some uncertainty as to their relevance for risk assessment of health effects resulting from environmentally relevant exposures.

15.3.1 Effects on the Respiratory System

15.3.1.1 Lung Injury and Inflammation

The 1999 Ozone SAD presented an overview of the effects of ozone inhalation on the lungs of laboratory animals. Acute effects were noted to include epithelial injury, increased airway permeability and inflammation in the upper and lower airways, along with a range of biochemical changes such as depletion of antioxidants and damage to polyunsaturated fatty acids and proteins. Given the high reactivity of ozone these reactions were expected to occur at the area of initial contact. It was hypothesized that the interaction of ozone with the lining of the lung initiated a reactive cascade, resulting in free radical generation and oxygenated biomolecules that penetrated into cells and mediated the biological effects of ozone. Morphological changes in the nasal cavity and nasopharynx had also been observed following both acute and chronic exposure. A study of nonhuman primates chronically exposed to 0.25 ppm ozone demonstrated that epithelial and interstitial changes in distal airways were the most striking morphologic alteration and appeared to persist over time. These changes involved the proliferation of non-ciliated bronchiolar and type II AECs and increased collagen localized in the peribronchiolar and centriacinar regions, effectively a remodelling of the centriacinar airways by extension of bronchiolar cell types in airways that were formerly alveolar ducts.

The US EPA 2006 Ozone AQCD further characterized the mechanisms behind the inflammatory and permeability changes resulting from ozone inhalation. Ozone was shown to interact with a wide range of cellular components, including polyunsaturated fatty acids, amino acid residues,

Table 15.3 Qualitative summary of ozone health effects in reviewed animal toxicology studies

Endpoint / target system	Animal models	Exposure range	Effects
Lung injury and inflammation	Normal mice and rats, NOS2 knockout mice, mouse strains with varying SP-D, SOD, or NF-κB expression levels	0.5–3 ppm	Formation of lipid oxidation products and other cellular damage leads to airway inflammation, epithelial injury and increased airway permeability; NF-κB and chemokines involved; antioxidant enzyme activities modulated; surfactant protein plays a protective role
Airway responsiveness	Normal mice, rats, guinea pigs and rabbits, mice deficient in CXCR2, IL-6 or TLR4	0.12–3 ppm	Heightened AHR with possible involvement of TLR4 and CXCR; studies with high exposure levels suggest that parasympathetic nerves, NO generation in the airways, altered calcium mobilization in airway smooth muscle, and increased permeability of the airway mucosa may also play a role
Experimental allergy	OVA-sensitized rats, mice and guinea pigs, postnatal mice co-exposed to LPS	0.1–2.5 ppm	Interaction with allergens exacerbates airway reactivity and increases immunologic and inflammatory responses (e.g. increased antibody production, aggravated allergic symptoms); equivocal results for longer-term exposure
Host defence	Mice	0.6 ppm	Impaired proliferation potential of splenic T-cells and natural killer cell activity
CNS	Rats, mice	0.25–1 ppm	Damaged or reduced neuron density, alterations in catecholamine levels, lipid peroxidation in brain tissue; effects may be associated with behavioural responses and acute effects on sleep–wake homeostasis; mechanism unclear but may be ROS-related; effects on postnatal development of the cerebellum and behavioural modifications following gestational exposure
Cardiovascular and other systemic responses	Rats, mice	0.25–1 ppm	Induction of iNOS expression and nitrotyrosine formation in the aorta, altered plasma biomarkers of endothelial function; suppressive response of genes related to energy metabolism in the liver, responses indicative of oxidative stress, NF-κB activation, and DNA replication and repair in lung and cutaneous tissue
Reproductive system and development	Rhesus monkeys, rats, mice	0.3–2.5 ppm	Structural alterations and possible effects on postnatal lung development; possible link between oxidative stress and adverse effects on germ cells and histopathological changes in the testes; gestational exposure linked to altered behaviour accompanied by changes in CNS levels of neurotrophins, and to cellular changes in the cerebellum
Genotoxicity and carcinogenicity	Guinea pigs, mice	0.45–1 ppm	Genotoxic effects observed at high exposure levels (DNA strand breaks in tracheobronchial epithelial cells, increased mutation frequency in splenic T-cells); no recent carcinogenicity studies
Susceptibility	Aged, immature and adult rats, rats with bleomycin-induced pulmonary fibrosis, rats on a low protein diet, rats with thyroxine-induced hyperthyroidism, obese mice	0.5–2 ppm	Increased sensitivity to ozone-induced oxidative stress in immature and aged vs. adult rats; greater ozone-induced decrease of serotonin in the cerebellum of malnourished rats; increased sensitivity to pulmonary inflammatory responses with hyperthyroidism; greater innate and ozone-induced airway reactivity responses with obesity

and a variety of low-molecular-weight compounds (e.g. GSH, urate, vitamins C and E). The interaction of ozone with lipids in the ELF or the epithelial cell membranes was shown to create ozonation products, which then stimulated airway epithelial cells, AMs, and neutrophils to release a host of pro-inflammatory mediators, including cytokines and chemokines (e.g. TNF- α , MIP-1 α , interleukins), ROS, eicosanoids, and platelet activating factor. The US EPA 2006 Ozone AQCD concluded that experimental animal studies provided extensive evidence that acute ozone exposure to levels as low as 0.1 to 0.5 ppm causes 1) lung inflammatory responses, typified by increased ROS, inflammatory cytokines, neutrophil influx, and activation of AMs; 2) damage to epithelial airway tissues; and 3) increased permeability of both lung endothelium and epithelium. Regarding long-term ozone exposure, the US EPA 2006 Ozone AQCD noted that animal toxicology studies continued to show chronic structural alterations in several areas of the respiratory tract including the centriacinar region. Morphologic evidence from studies using exposure regimens that mimicked seasonal exposure patterns indicated increased lung injury in comparison with conventional stable chronic exposure regimens. It was noted that infant rhesus monkeys repeatedly exposed for 8 h/d to 0.5 ppm ozone over 11 episodes exhibited abnormalities in the tracheal basement membrane, eosinophil accumulation in conducting airways, decrements in airway innervation and remodelling of the distal airways. Evidence up to that time also indicated that long-term exposure of rats to ozone could cause mucous cell metaplasia and hyperplasia in the nasal epithelium.

Recent toxicology studies have contributed to the mechanistic evidence base for explaining the processes involved in ozone-induced lung injury and inflammation. In work by Kenyon et al. (2002, 2006), mutant mice lacking inducible NOS2 (NOS2^{-/-}) were more susceptible to ozone-induced lung inflammation and injury than their wild-type counterparts, indicating that this enzyme may have a protective effect against lung injury caused by acute ozone inhalation (1 ppm). They hypothesized that NO, generated from NOS2 either in airway epithelial cells or bone-marrow-derived inflammatory cells, was responsible for the protective effect of NOS2. Chimeric NOS2^{+/-} mice, which had bone marrow from NOS2^{-/-} mice transplanted into C57BL/6 recipients, had a significantly greater response to ozone (increased lung lavage neutrophils and decreased exhaled NO concentrations) compared with the reciprocal chimeric strain (NOS2^{+/-}). These results contrast with those of two previous studies using the NOS2 knockout C57BL/6 mouse model, which reported that mice deficient in NOS2 were resistant to the lung inflammation and tissue injury observed in wild-type mice following acute exposure to 0.8 ppm ozone (Fakhrzadeh et al., 2002; Laskin et al., 2002). These earlier studies used a shorter exposure duration and a slightly lower dose, raising the possibility that the involvement of NOS2 in the response to ozone may depend on exposure concentration and duration.

Ozone is known to react with substrates in the ELF, including ascorbic acid, uric acid, glutathione, proteins and unsaturated lipids. This likely prevents the diffusion of ozone to the underlying epithelium, but oxidation products formed by the reaction of ozone with lipids in the ELF are believed to play a role in ozone-induced damage to the lung epithelium. Pulfer et al. (2005) observed formation of the cholesterol oxidation products β -epoxide and 6-oxo-3,5-diol in the lungs of an ozone-sensitive mouse strain (female C57BL/6J mice) acutely exposed to 0.5, 1, 2 or 3 ppm ozone for 3 h, with this effect being dose-dependent for 6-oxo-3,5-diol. *In vitro*, 5 β ,6 β -epoxycholesterol was reported to be a major product of the reaction of ozone with isolated BAL or intact cultured 16-HBE human bronchial epithelial cells (Pulfer and Murphy, 2004). The reaction of this epoxide with lung epithelial cells yielded abundant levels of cholestan-6-oxo-3 β ,5 α -diol. Both oxysterols were cytotoxic to cultured cells, possibly due to their ability to inhibit cholesterol biosynthesis. Ballinger et al. (2005) examined how ozone interaction with ELF may induce cellular damage using a red cell membrane (RCM) *in vitro* model to mimic the lung surface. Exposure of RCMs to ozone produced reaction products with ascorbic acid and glutathione, and these products were believed to initiate oxidation that could

account for the permeation of ozone through the ELF. Thus recent *in vivo* and *in vitro* research supports previous assumptions that ozone will react with target molecules in the lipid-rich pulmonary ELF.

Surfactant protein (SP) plays an important role in innate immunity and regulation of the lung inflammatory response (Janic et al., 2005). SP-A is expressed by type II AECs and regulates surfactant (phosphatidylcholine) secretion by these cells. Wang et al. (2004) examined the *in vitro* response of human variants of SP-A to ozone-induced oxidation. Ozone was observed to induce oxidization of several amino acid residues (including cysteine, methionine and tryptophan), which may contribute to structural differences (oligomerization and/or aggregation) that alter SP-A function. In the absence of ozone, the SP-A2 variant inhibited adenosine-5'-triphosphate (ATP)-stimulated surfactant secretion from alveolar type II cells to a greater extent than the SP-A1 variant. Again, ozone treatment significantly reduced the ability of these proteins to inhibit surfactant secretion. In other research, cytokine production and NF- κ B signalling were studied in THP-1 cells following *in vitro* exposure to ozone with or without SP-A obtained from BAL of patients with alveolar proteinosis (Janic et al., 2005). Ozone significantly reduced TNF- α and IL-8 production by THP-1 cells in response to SP-A, and also decreased the ability of SP-A to activate NF- κ B signalling. Thus the oxidation of SP-A could be a mechanism by which ozone affects macrophage function. Kierstein et al. (2006) found a protective role for SP-D, a potent immunoregulator, following acute exposure of mouse strains with genetically different expression levels of SP-D, although this study used a very high ozone exposure level (3 ppm).

Several recent studies examined the relationship between ozone exposure and oxidative stress. The administration of vitamin E was found to protect against oxidative stress in rats chronically exposed to 0.5 ppm ozone as determined by a reduction in plasma content of acute phase proteins (induced by inflammatory cytokines) and decreased lysozyme activity associated with enhanced macrophage activity (Jakubowski et al., 2004). *In vitro*, the activities of antioxidant enzymes G6PDH, SOD, GPx, and GRx in Jurkat human T lymphoma cells were stimulated by exposure to ozone, with the response being dependent on the enzyme and ozone dose (Larini et al., 2003). Otto-Knapp et al. (2003) reported ozone-induced stimulation of epithelial GSH-peroxidase and SOD in tissue cultures of normal human nasal mucosa. In tissue cultures isolated from the nasal mucosa of GSTM1-deficient patients, enhanced SOD activity was observed above that in normal tissue cultures (GSTM1 carriers), suggesting that a deficiency in GSTM1 may affect the regulation of antioxidant enzymes in response to ozone exposure. Lee et al. (2003) observed that exposure of SOD, catalase and GSH-peroxidase to ozone in solution resulted in the inactivation of these enzymes. Both GSH and ascorbate were effective at protecting SOD from ozone-induced inactivation and, unless depleted by severe oxidative stress, these cellular antioxidants would be expected to protect antioxidant enzymes from ozone-induced inactivation.

Mice over-expressing SOD were protected against the lung inflammation and tissue damage observed in wild-type mice following a 3-h acute exposure to 0.8 ppm ozone (Fakhrzadeh et al., 2004a), while another study reported that mice lacking extracellular SOD exhibited an increased inflammatory response following exposure to 1.5 ppm ozone for 48 h (Jonsson et al., 2002). These studies indicate that SOD plays a role as a modulator of ozone-induced inflammatory reactions, likely by controlling levels of superoxide anion and possibly also through regulation of the transcription factor nuclear factor kappa B (NF- κ B) and downstream gene products involved in the production of inflammatory mediators. The NF- κ B transcription factor is responsible for the regulation of inflammatory genes involved in ozone toxicity, including those for nitric oxide synthase 2 (NOS2), cyclooxygenase-2 (COX-2), and TNF- α . Consistent with the important role of NF- κ B, mice lacking the NF- κ B p50 protein were shown to be protected from lung inflammation and tissue injury following acute exposure to 0.8 ppm ozone (Fakhrzadeh et al.,

2004b). In another study, the chemokines CXCL1,2,3, CXCL10, CCL3, CCL7 and CCL11 were found to be associated with ozone-induced neutrophilic airway inflammation immediately post-exposure in mice following inhalation of 0.8 ppm for 6 h as demonstrated by upregulation of mRNA for these proteins (Michalec et al., 2002). CXCL10, CCL3, and CCL7 mRNA levels were sustained 18 h post-exposure, and ozone also increased lung protein levels of CXCL10, CCL7, and CCR3 (CCL7R). Exposure of mice to 0.2 ppm ozone for 6 h did not produce a similar chemokine response.

The role of AMs in ozone-induced inflammation and toxicity continues to be explored *in vitro*. Acute exposure of isolated THP-1 cells (a human macrophage-like cell line) to ozone resulted in NO and H₂O₂ production and cell injury reflected by increased LDH levels (Klestadt et al., 2002). Foucaud et al. (2006) reported ozone-induced modification of the redox status of THP-1 cells as reflected by lipid peroxidation, increased HO-1 expression, elevated H₂O₂ concentration, and reduced GSH content. Janic et al. (2003) found a small decrease in the viability of THP-1 cells following ozone exposure; however, the functional integrity of the cells as measured by the expression of the cell surface proteins CD14 and CD11b was not affected. In contrast, Klestadt et al. (2004) reported a dose-related reduction in surface membrane markers on THP-1 cells—especially CD13 and CD14—following acute ozone exposure, an effect they attributed to ozone-induced membrane rearrangement.

In other mechanistic studies, Ahmad et al. (2005) provided evidence of ozone-induced ATP release from four different human lung epithelial cells and one rat alveolar type I cell. This response is believed to be a protective mechanism, as extracellular ATP is a signalling molecule that influences numerous cellular functions in preventing ozone-induced cell death. Wang et al. (2006) determined the gene expression responses of rat alveolar type I and type II cells following acute *in vitro* ozone exposure. Ozone increased the expression of genes involved in stress and inflammatory responses and decreased the expression of genes involved with antioxidant defence, the extracellular matrix, fluid transport, lipid metabolism and cellular differentiation. These changes were more prominent in type I cells, which were more sensitive to ozone-induced injury than type II cells. Alveolar type II cells showed higher levels of expression of SP than type I cells, which may serve to protect them from ozone. Manzer et al. (2006) also found that rat alveolar type I cells were more sensitive than type II cells to ozone-induced injury following *in vitro* exposure. Nadadur et al. (2005) generated gene expression profiles for rat lung tissue following acute *in vivo* ozone exposures and reported increased expression levels of genes involved in cell proliferation, DNA damage repair and the stress response; however, very high ozone exposure concentrations were used in this study (2 or 5 ppm).

15.3.1.2 Pulmonary Function and Airway Responsiveness

Pulmonary endpoints such as FVC were briefly discussed in the 1999 Ozone SAD. Increased airway responsiveness was generally considered to be a consequence of ozone-induced inflammation; however, there were indications that ozone was capable of increasing airway responsiveness and damaging airway epithelium in the absence of neutrophilia and microvascular leak. The US EPA 2006 Ozone AQCD noted that animal studies had provided extensive evidence that acute ozone exposures altered breathing patterns so as to cause rapid shallow breathing (i.e. increased breathing frequency and decreased tidal volume), an effect that appeared to attenuate after several days of exposure. New research had shown that rapid, shallow breathing in response to ozone caused a more evenly distributed injury pattern, rather than protection from injury as previously thought. Decreased lung volumes were observed in rats following acute exposure to 0.5 ppm ozone, while exposures of ~1 ppm affected breathing compliance and resistance. Exposures were also observed to create a pattern of attenuated pulmonary function decrements in rats without concurrent attenuation of lung injury and

morphological changes, indicating that the attenuation in pulmonary function responses did not result in protection against all the effects of ozone. Data from inbred mouse strains with varying ventilatory responses to ozone suggested that 1) the control of ventilatory response is determined, at least in part, by genetic factors; 2) increased V_t in some strains may contribute to lung injury due to a greater dose of ozone reaching the lower lung; 3) the ability of some strains to reduce body temperature may account for their resistance to ozone-induced lung injury; and 4) tracheal transepithelial potential is determined, in part, by genetic factors. Importantly, the genetic loci that appeared to be modulating various aspects of pulmonary responses to ozone differed from each other and from loci controlling inflammatory responses.

The US EPA 2006 Ozone AQCD discussed the heightened airway responsiveness (or reactivity) observed in various animal models following acute exposures to 0.5–1 ppm ozone. Ozone had been shown to increase AHR to nonspecific bronchoconstrictive agents (e.g. ACh, MCh, histamine, carbachol) administered to laboratory animals by inhalation or intravenous routes. There appeared to be a temporal relationship between inflammatory cell influx and ozone-induced AHR, but inflammation was not a prerequisite for AHR. Repeated ozone exposures were found to enhance this response, possibly by modulating rapidly adapting airway receptors or by altering the structure of conducting airways. Ozone-induced AHR was noted to persist longer and attenuate more slowly than pulmonary function decrements and respiratory symptom responses.

Experimental animal research continues to examine the relationship between ozone exposure and pulmonary function responses, especially AHR, a characteristic of human asthma. The link between inflammatory mediators and pulmonary function is a key theme in this area. Work by Johnston RA et al. (2005a) suggested that CXCR2, a receptor for neutrophil chemotactic factors, played a role in AHR and acute infiltration of neutrophils in mice exposed to ozone. Exposure to 1 ppm ozone for 3 h increased AHR in CXCR2-deficient mice and wild-type BALB/cJ mice at 3 h post-exposure. By 24 h, AHR was sustained in wild-type mice but had returned to normal in CXCR2-deficient mice. There were no significant differences in chemokine expression between mouse strains; however, a more pronounced increase in neutrophil and epithelial cell content of BALF was reported for wild-type vs. CXCR2-deficient mice at 24 h post-exposure. In another study, the role of IL-6 in airway injury, inflammation, and AHR was determined in wild-type and IL-6-deficient mice exposed to ozone (Johnston RA et al., 2005b). IL-6 deficiency resulted in reduced airway neutrophilia and reduced sTNFR1 and/or sTNFR2 expression following a 72-h exposure to 0.3 ppm ozone. IL-6 deficiency did not affect AHR to MCh as measured by the outcome indicator Penh following acute ozone exposures, but it did appear to protect against an increased end expiratory pressure response. Studies conducted by Jang and colleagues examined the effect of ozone exposure on AHR as measured by Penh and demonstrated a dose-related increase in this parameter following exposure of mice to 0.12, 0.5, 1 and 2 ppm ozone for 3 h with the greatest response occurring immediately post-exposure (Jang et al., 2003a, 2003b, 2005b). Hollingsworth et al. (2004) examined the role of TLR4 in pulmonary responses to ozone using TLR4-deficient (TLR4-) and wild-type (TLR4+) mice. Exposure to 0.3 ppm ozone for 72 h produced lung inflammation in both TLR4+ and TLR4- mice, while increased airway responsiveness was only observed in TLR4+ mice.

A number of recent studies using very high ozone exposure concentrations highlight some possible mechanistic toxicological pathways (though at the same time, it is necessary to recall the uncertainty as to the relevance of these results to the assessment of health risks from exposure to ambient concentrations of ozone). DeLorme et al. (2002) correlated a peak in lung inflammation at 3 h following acute exposure of rats to 2 ppm ozone with AHR measured as airway resistance to MCh. The induction of neutropenia prior to ozone exposure protected against AHR, suggesting a role for neutrophils in the AHR response of rats. In contrast, Park et

al. (2004a) reported that acute 2 ppm ozone exposure produced AHR in response to MCh that involved complement activation but was independent of neutrophils or mast cells. The role of IL-1 β in airway inflammation and hyperresponsiveness was examined by Park et al. (2004b) in mice exposed to 2 ppm ozone for 3 h. Ozone-induced effects on AHR, neutrophil inflammation and respiratory epithelial cell damage were shown to involve the induction of IL-1 β , which was prevented by administration of the IL-1 receptor antagonist IL-1Ra. Another study reported that exposure of mice to 2 ppm ozone markedly elevated the amount of neuronal NOS protein in airway tissue homogenates and increased nitrate concentration in BALF, indicating NO generation in the airways, which could play a role in the AHR observed following exposure (Jang et al., 2003b). Toward and Broadley (2002) examined the effects of acute exposure to 2 ppm ozone on airway function, cell infiltration and NO generation in guinea pigs and the modification of these effects by two anti-inflammatory agents: the corticosteroid dexamethasone and the phosphodiesterase-4 inhibitor rolipram. Ozone exposure produced early-phase (associated with a decrease in NO metabolites) and late-phase (coinciding with increased NO metabolites, respiratory rate, and lung macrophage and eosinophil content) bronchoconstriction indicated by a fall in specific airways conductance measured by whole body plethysmography. Treatment with anti-inflammatory agents inhibited AHR resulting from ozone exposure but did not affect airway function changes.

The role of nerves and airway smooth muscle in the effects of ozone on lung responsiveness has recently been investigated. Yost et al. (2005) studied bronchoconstriction responses indicative of AHR and effects on the lung eosinophil population in guinea pigs following a 4-h exposure to 2 ppm ozone. Ozone increased eosinophils in BALF, in the airways and in the vicinity of airway nerves on d 1 and 3 post-exposure, while d 2 levels were comparable to controls. The AHR response to vagal (parasympathetic) nerve stimulation was significantly greater in ozone-exposed guinea pigs compared with controls. AHR appeared to be mediated at the level of the parasympathetic nerves on d 1 and 2 post-exposure, then at the level of the airway smooth muscle on d 3. Eosinophils produced on d 3 were not associated with vagal AHR and may actually play a beneficial role, as their depletion resulted in a greater vagal AHR response. The involvement of intrapulmonary neuropeptides in AHR development (measured as airway resistance) was determined in rabbits following acute (1 h/d) and repeated (1–8 d) exposure to 2 ppm ozone (Ren et al., 2004). Results indicated that the levels of vasoactive intestinal peptide (VIP) and calcitonin gene-related peptide (CGRP) correlated with the development of AHR. Ozone-induced AHR may result, at least in part, from increased permeability of the airway mucosa. Fu et al. (2002) demonstrated that tachykinin neuropeptides (substance P and neurokinin A) may be involved in the increased permeability of the tracheal mucosa in guinea pigs acutely exposed to 3 ppm ozone for 30 min.

The effect of a high ozone exposure level (3 ppm for 2 h) on the hyperresponsiveness of guinea pig airway smooth muscle to histamine was determined by ex vivo assessment of intracellular calcium mobilization in relation to tracheal smooth muscle contractility (Yoshida et al., 2002). Ozone exposure appeared to directly affect airway smooth muscle by altering calcium mobilization in increasing the activity of the calcium refilling pump and releasing channels on the sarcoplasmic reticulum. *In vitro*, Wu et al. (2003) found that exposure of cultured ferret trachea depleted of sensory innervation to ozone induced AHR by enhancing tracheal smooth muscle responsiveness. This response was mediated through the release of substance P from intrinsic airway neurons, which facilitated ACh release from cholinergic nerve terminals. Ozone exposure was also observed to produce significant increases in the number of substance P-positive neurons in longitudinal trunk ganglia, the extent of substance P innervation to superficial muscular plexus nerve cell bodies, and the density of substance P nerve fibres in tracheal smooth muscle.

15.3.1.3 Experimental Allergy

Experimental allergy models were not described in the 1999 Ozone SAD. Research in this area subsequently expanded, and the OVA-sensitized guinea pig became a commonly used model. The US EPA 2006 Ozone AQCD discussed the interaction of ozone exposure with specific biological agents in increasing airway reactivity. These studies provided evidence that ozone could augment antigen-induced AHR in sensitized laboratory animals, and were consistent with the ozone-induced exacerbation of AHR reported in atopic humans with asthma. Studies have shown that AHR in asthmatics is due in part to chronic inflammation and airway remodelling, and that AHR can be induced by specific antigens as well as ozone. The US EPA 2006 Ozone AQCD noted that the results of animal studies were difficult to extrapolate because of interindividual and interspecies differences in responsiveness to bronchoprovocation, and the possible adaptation of airway responsiveness with long-term, repeated ozone exposures.

Researchers using experimental allergy models have continued to examine the interaction of ozone exposure with allergens such as OVA in sensitized rats, mice and guinea pigs. In two sets of studies, Koike and colleagues examined the effects of exposure to 1 ppm ozone for 72-h or repeated exposures to 0.3, 0.56 or 1 ppm ozone for 3 d every 2 weeks on antigen-presenting activity of lung cells in OVA-sensitized rats (Koike and Kobayashi, 2004; Koike et al., 2004). An increase in antigen-presenting activity of whole lung cells and lung dendritic cells was reported in OVA-sensitized rats acutely exposed to 1 ppm ozone, compared with air-exposed sensitized rats, as a result of increased expression of cell-surface molecules and antigen-presenting cells in the lung (Koike and Kobayashi, 2004). Repeated exposure of OVA-sensitized rats increased antigen-presenting activity of BAL cells and expression of Ia antigen and co-stimulatory molecules at 0.56 and 1 ppm ozone, increased inflammatory cell infiltration at 0.3, 0.56 and 1 ppm ozone, and increased AHR at 1 ppm ozone in response to OVA challenge, compared with effects on air-exposed sensitized rats (Koike et al., 2004). These results suggested that increased antibody production following exposure of allergen-sensitized rats to ozone could exacerbate antigen-induced AHR and allergic symptoms.

Distinct early response mechanisms were observed in postnatal mice following acute exposures to LPS and/or ozone (Johnston CJ et al., 2006). Exposure to 1 or 2.5 ppm ozone for 4 h dose-dependently increased c-jun and c-fos mRNA in the lungs of 4-, 10-, and 56-d-old mice and induced TLR4 mRNA in 10- and 56-d-old mice. LPS alone induced c-jun, c-fos, TLR2, and TLR4 mRNA in 10- and 56-d-old mice at 30 min post-exposure, but no induction was detected in 4-d-old mice. These results suggested that exposure to ozone and LPS individually or in combination may regulate gene expression by activating early response signalling pathways operating through somewhat differing transcription factor profiles.

Several studies have investigated experimental allergy models using longer-term exposure regimens. Iijima and Kobayashi (2004) studied the effects of subchronic ozone exposure on the aggravation of allergy-like reactions following repeated nasal OVA challenges in sensitized guinea pigs. Exposure to levels of ozone ranging from 0.1 to 0.6 ppm for 24 h/d, 6.5 d/week over 5 weeks aggravated allergic responses to OVA (sneezing and nasal secretion) and also increased immune-based inflammatory responses and production of anti-OVA-immunoglobulin G (IgG), compared with air-exposed OVA-sensitized guinea pigs. Benchmark concentrations calculated at the 95% lower limit corresponding to an additional 10% risk of ozone-induced enhancement of nasal allergy-like symptoms ranged from 0.06 ppm ozone for sneezing responses to 0.14 ppm ozone for eosinophil infiltration into the epithelium and subepithelium. In another study, subchronic exposure of OVA-sensitized C57BL/6 mice to 1 ppm ozone for 6 h/d, 5 d/week for 5 weeks increased immune-based inflammatory responses and respiratory resistance and decreased dynamic compliance compared with air-exposed sensitized mice (Funabashi et al., 2004).

A variety of exposure protocols were used by Last et al. (2004) to examine the effects of ozone on airway remodelling and inflammation in OVA-sensitized BALB/c mice. They observed increased airway collagen content and goblet cell hyperplasia in mice exposed concurrently to OVA and ozone for 6 weeks. Greater hyperplasia was observed following exposure to 0.2 vs. 0.5 ppm ozone, and the airway remodelling effects of ozone plus OVA were generally additive. Ozone exposure decreased the OVA-induced accumulation of inflammatory cells in the lung, particularly with concurrent OVA plus ozone exposure protocols. This effect of subchronic ozone exposure contrasts with the increased immune-based inflammatory responses in OVA-sensitized mice observed by Funabashi et al. (2004). Last et al. (2004) suggested that the decrease in OVA-induced inflammation was due to the induction by ozone of a cell-mediated (Th1) immune response that counteracted the humoral immune response (Th2) induced by OVA. Alternatively, migration of inflammatory cells into the airway submucosal space may have occurred, which would explain their lack of detection in BALF and would not indicate an antagonist effect of ozone.

Harkema and Wagner (2005) reviewed a series of rodent studies concerning the effects of co-exposure to ozone and biogenic substances on airway surface epithelial cells. They concluded from these data that biogenic substances appeared to intensify ozone-induced epithelial and inflammatory responses, while ozone exacerbated the AHR response to bacterial endotoxin or OVA. Ozone and endotoxin were both capable of producing mucous cell metaplasia (MCM) in the rat respiratory tract, albeit at different locations (nasal and respiratory epithelium, respectively), with each enhancing the effect of MCM produced by the other. Neutrophil depletion was shown to inhibit MCM at both locations, suggesting a role for neutrophils in its development.

Less relevant to the discussion are recent studies that used high ozone exposure levels. Acute exposure to 2 ppm ozone for 3 h increased airway responsiveness to OVA (measured as Penh) and airway inflammation in sensitized BALB/c mice (Jang et al., 2004). Ozone also downregulated pulmonary iNOS expression and upregulated eNOS and nNOS (neuronal NOS) expression, effects that were associated with neutrophilic and eosinophilic airway inflammation. In contrast to these results and those of the acute study by Funabashi et al. (2004) discussed above, Jang et al. (2006) reported that chronic exposure of OVA-sensitized BALB/c mice to 2 ppm ozone for up to 12 weeks decreased respiratory resistance to OVA (measured as Penh) compared with air-exposed controls. Chronic ozone exposure also produced airway remodelling in mice similar to that reported by Last et al. (2004) above, involving an increased number of goblet cells and elevated collagen content in the lung indicative of a stiffened airway. The authors hypothesized that airway remodelling may have protected against AHR and mucosal dehydration.

15.3.2 Effects on Host Defence

The 1999 Ozone SAD noted a number of adverse effects on host defence following short-term ozone exposures, including damaged mucociliary clearance cells, impaired AM phagocytotic ability, reduced lung clearance, decreased numbers of T- and B-lymphocytes, and impaired antiviral response. It was stated that bacterial challenge interacted with ozone exposure to increase mortality in mice, which was thought to be due to an adverse effect of ozone on macrophage function. This increased mortality was more likely to occur when ozone exposure preceded the administration of bacteria. The 2006 US EPA Ozone AQCD stated that findings from several more recent studies evaluating the effects of ozone on resistance to infectious microorganisms were in concurrence with those from earlier studies, showing generally

increased mortality and morbidity, decreased lung clearance, increased bacterial growth, and increased severity of infection at exposure levels of 0.1–1 ppm ozone for 1 week.

There appears to be substantial evidence that acute ozone exposure can increase the susceptibility of laboratory animals to infectious diseases due to modulation of lung host defences. Disruption of AM function likely plays an important role. Phagocytosis by these cells is inhibited at concentrations ranging from 0.1 to 1.2 ppm ozone, returning to control levels if exposures are repeated for several days. Other changes observed in AMs at this environmentally relevant concentration range and indicative of mechanisms at play include superoxide radical formation, altered chemotaxis/motility, decreased interferon- γ levels, decreased lysosomal activity, increased prostaglandin E levels, and increased expression of iNOS mRNA and protein. Mucociliary clearance is affected in most test species at just under 1 ppm, with lower levels (~0.1 ppm) increasing clearance and somewhat higher levels decreasing clearance. The US EPA 2006 Ozone AQCD noted that ozone may enhance or suppress immune responsiveness depending on exposure concentration, species, route of allergen exposure, and timing of exposure. Immune responses are generally impaired for the first several days of continuous exposure, followed by an adaptation to ozone that allows the return of normal responses. Studies of mouse strains with genetically determined differential sensitivity or resistance to ozone indicated a possible interaction between the innate and acquired immune systems, supporting the notion that ozone may shift the immune response toward a Th2-like pattern.

In recent work, ozone-related immune dysfunction was studied in mice exposed for 10 h/d to 0.6 ppm ozone for 15 or 27 d (Feng et al., 2006). Ozone increased thymic MNC proliferation of CD4-CD8-thymocytes in response to IL-7 stimulation, and decreased natural killer cell activity and T-cell proliferation by splenic MNCs in response to OVA, indicating impairment of innate and acquired immune functions. Antioxidants (catechin and black tea extract) protected against the decrease in T-cell proliferation, suggesting this response was mediated by oxidative damage following the reaction of ozone with biomacromolecules. These results demonstrated that ozone could impair both the natural killer cell activity and the proliferation potential of splenic T-cells to a specific antigen stimulus. N-formyl-methionyl-leucyl-phenylalanine (fMLP) is a peptide chemoattractant isolated from bacterial culture suspensions. Klestadt et al. (2005) found that pre-exposure of THP-1 cells to ozone had an inhibitory effect on the activation of cell movement and NO production by fMLP in these model macrophage cells. Ozone also amplified the liberation of H₂O₂ induced by fMLP, while NO was not affected by ozone pre-exposure but was dose-dependently decreased following combined exposure. These results suggested ways by which ozone may affect the ability of macrophages to respond to microbial challenge. Other recent studies on the effects of ozone on AM function are described in Section 15.3.1.2. Aside from the studies above, no new published research was identified on host defence and the effects of ozone on resistance to infection.

15.3.3 Systemic Effects beyond the Pulmonary System

15.3.3.1 Effects on the Central Nervous System

Research on the effects of ozone on neurological endpoints was not identified in the 1999 Ozone SAD, but work had progressed in this area by the time of the US EPA 2006 Ozone AQCD. Neurobehavioural effects had been reported in a number of studies over a concentration range of 0.2–1 ppm ozone, including short- and long-term memory deficits, increased freezing behaviour, and decreased motor activity and exploratory behaviour. These effects were associated with increases in reactive oxygen/nitrogen species and ozonation products, altered neurotransmitter levels, morphological changes in several brain regions, and altered

electroencephalogram (EEG) patterns during sleep. Studies with rats had also found evidence of alterations to visual and olfactory neural pathways at ozone concentrations of >1 ppm, as well as morphological and hormonal changes in the pituitary–thyroid–adrenal axis at ~0.75 ppm. However, the mechanisms underlying these neurological effects were little understood.

Recent studies in experimental animals have added to the body of evidence suggesting that inhalation of ozone may lead to oxidative stress and neuron dysfunction in the CNS with associated behavioural effects. Acute exposure of rats to 1 ppm ozone produced morphological effects in the granule cells of the olfactory bulb, including a loss of dendritic spines at 2 h, 24 h and 10 d post exposure, and ultrastructural changes including vacuolation, mitochondrial edema and endothelial damage at 2 and 24 h (Colin-Barenque et al., 2005). Recovery from these effects generally occurred by 15 d post-exposure. The loss of dendritic spines was suggested to be the consequence of strong synaptic activation involving Ca²⁺ influx and ROS generation, while the ultrastructural changes may have been related to ozone effects on membrane permeability. Soulage et al. (2004) evaluated the influence of acute inhalation of 0.7 ppm ozone on catecholamine biosynthesis and utilization rate in discrete brain regions (cortex, striatum, hypothalamus, A2 and A6 noradrenergic cell groups), sympathetic target organs (heart and lungs), and in the superior cervical ganglia of rats. Catecholamine biosynthesis was significantly stimulated in superior cervical ganglia and the caudal A2 subset, while catecholamine turnover was significantly increased in the heart and cortex but inhibited in the lungs and striatum. The regional specificity of these changes argues against a cytotoxic influence of ozone on catecholamine neurons.

Escalante-Membrillo et al. (2005) reported that acute exposure of rats to 1 ppm ozone produced differing levels of oxidative stress measured as lipid peroxidation in the cortex, striatum, midbrain, thalamus, hypothalamus, and pons regions of the brain. Some brain regions appeared better able to tolerate ozone-induced oxidative stress, possibly due to a differential distribution of pro-oxidant molecules (such as Fe and ascorbic acid) and/or antioxidant enzymes (e.g. SOD, catalase, and GPx). Evidence of increased lipid peroxidation in the cortex, pons, thalamus and hypothalamus indicates that free radicals may disturb the neuronal nuclei found in these regions, which may explain sleep-related and other CNS effects attributed to ozone. In another study, a high dose of the antioxidant vitamin E prevented ozone-induced increases in catecholamine levels in the striatum of rats acutely exposed to 1 ppm ozone, suggesting that the effects of ozone on brain catecholamine levels are mediated by free radicals (Gonzalez-Pina et al., 2002).

Subchronic exposure of rats to 0.25 ppm ozone for 4 h/d on weekdays for 7, 15, 30 or 60 d produced dopaminergic neuron dysfunction and nigral lipid peroxidation and cell death (Angoa-Perez et al., 2006). These effects were counteracted by treatment with 17 β -estradiol, suggesting the possible involvement of oxidative stress given the antioxidant properties of this compound. In another study, exposure of rats to 0.25 ppm ozone for 4 h/d for 15 or 30 d produced cell death of the dopaminergic neurons in the substantia nigra and striatum, associated with reduced motor activity, increased lipid peroxidation levels and progressive morphological alterations including edema, neuronal cytoplasmic vacuolization and damage to the neuropile (Pereyra-Munoz et al., 2006). Increased iNOS and SOD immunoreactivity was detected in the striatum and substantia nigra, and increased adenosine 3',5'-monophosphate-regulated phosphoprotein of 32 kD (DARPP-32) immunoreactivity was found in the striatum, as well as increased phosphorylation signalling.

Changes in the behaviour of adult male mice as measured by inter-male agonistic patterns and social investigation were reported following gestational exposure to ozone at 0.3 or 0.6 ppm (Santucci et al., 2006). Mice exposed to either ozone concentration showed a significant increase in freezing posture and a decrease in nose-sniffing behaviour, although no dose-

response was evident. These behavioural changes were accompanied by alterations in CNS levels of neurotrophins, including a decrease in hippocampal nerve growth factor (NGF) in the 0.6 ppm group and increased brain-derived neurotrophic factor (BDNF) in the striatum of both dose groups. BDNF promotes survival and differentiation of dopaminergic neurons, and enhanced BDNF in the striatum may be associated with changes in dopamine and in behavioural activity related to this neurotransmitter, including locomotor and aggressive behaviour. Romero-Velazquez et al. (2002) reported that prenatal ozone exposure resulted in adverse effects on the postnatal development of the cerebellum in rats. Exposure of pregnant dams to 1 ppm ozone throughout gestation decreased the total area and number of Purkinje cell neurons in the cerebella of male offspring compared with offspring from unexposed dams, an effect that could lead to permanent damage in the cerebellum.

Recent studies have reported that acute ozone exposure can affect sleep patterns in rats. Exposure of rats to 1 ppm ozone for 24 h increased the total time spent in slow wave sleep while decreasing rapid eye movement (REM) sleep, also known as paradoxical sleep (Rubio and Paz, 2003). Pretreatment with the cyclooxygenase inhibitor indomethacin, which blocks arachidonic acid metabolism and prostaglandin synthesis, reduced the ozone-associated decrease in REM sleep, supporting a role for inflammatory mediators in this effect. In another study, ozone-induced disruptions of serotonergic activity were determined by measurements of 5-hydroxyindolacetic acid (5-HIAA), the primary breakdown product of serotonin, in the dorsal raphe and hypothalamic MPA, structures involved in the sleep–wake homeostasis of rats (Gonzalez-Pina and Alfaro-Rodriguez, 2003; Gonzalez-Pina et al., 2003). The ozone exposure regimen followed a bell-shaped diurnal pattern over a 7 a.m. to 7 p.m. period with ozone concentrations peaking at 12 p.m. (0.5 ppm) and dropping to 0 ppm by 7 p.m, mimicking pollution levels observed in cities. Exposure produced increased extracellular 5-HIAA concentrations in the dorsal raphe that correlated with a decrease in paradoxical REM sleep. The authors suggested that the decrease in REM sleep was the behavioural expression of ozone-induced disruptions of the modulation of serotonergic activity by dorsal raphe. Ozone decreased extracellular 5-HIAA concentrations in the hypothalamic myeloperoxidase (MPO), which correlated with a decrease in slow wave sleep and an increase in wakefulness during the 12-h dark post-exposure phase (7 p.m. to 7 a.m.). These post-exposure effects were attributed to the hypothalamic role in the sleep–wake cycle (Gonzalez-Pina and Alfaro-Rodriguez, 2003). In further research the role of ACh release in the hypothalamic MPO area during the sleep–wake cycle was examined (Alfaro-Rodriguez and Gonzalez-Pina, 2005). Continuous exposure of rats to 0.5 ppm ozone for 24 h increased slow wave sleep and decreased the time spent in REM sleep, similar to the results reported by Rubio and Paz (2003). Comparison of the pre-exposure light phase period with the exposure light phase period indicated a decrease in ACh with a concomitant decrease of time spent in REM sleep. In the absence of ozone exposure, ACh release in the hypothalamic MPO followed a circadian rhythm.

15.3.3.2 Cardiovascular and Other Systemic Effects

The systemic extrapulmonary effects of ozone were not a major research focus at the time of the 1999 Ozone SAD. This document mentioned several cardiovascular effects of ozone reported in rodents, including decreases in heart rate, arterial blood pressure and core temperature, and increased frequency of arrhythmia. The potential for significant extrapulmonary responses was better recognized by the time of the US EPA 2006 Ozone AQCD, which stated that ozone may indirectly affect organs beyond the respiratory system via the transport of reaction products in the bloodstream to target sites, or from exposure-related production of mediators, metabolic products or cell trafficking. Evidence was emerging that provided considerable plausibility to how exposure to ozone might impact the cardiovascular system. A number of experimental animal studies had demonstrated an ozone-induced

hypothermic response involving decreased heart rate, mean arterial pressure and core temperature with exposure levels in the range of 0.1–0.5 ppm. Direct ozone effects such as the release of platelet activating factor (PAF) from lung epithelial cells could potentially contribute to blood clot formation, increasing the risk of serious cardiovascular outcomes. It was also recognized that the interaction of ozone with surfactant components in the lung ELF may result in the production of oxysterols and reactive oxygen species that could exert cytotoxic effects on lung and heart cells and/or exhibit PAF-like activity by contributing to clotting. It was hypothesized that indirect ozone effects such as the stimulation of vasoconstrictor secretion or effects on neuronal reflexes could result in increased arterial blood pressure and/or altered electrophysiologic control of heart rate or rhythm.

In discussing other extrapulmonary systemic effects, the US EPA 2006 Ozone AQCD stated that some studies had shown an effect of ozone on liver xenobiotic enzymes at concentrations as low as 0.1 ppm, while other studies had shown no alterations in metabolic enzymes even at 1 ppm, with the effects appearing to be highly species-specific. Effects of ozone on spleen and thymus were observed only at high concentrations (>1 ppm); similarly effects on cutaneous and ocular tissue were only observed at high concentrations that were not relevant to the ambient environment.

Recent research on cardiovascular endpoints is limited. Sanchez-Gonzalez et al. (2004) reported that exposure of rats to 0.25 ppm ozone over 28 d induced iNOS expression and nitrotyrosine formation in the aorta, a marker for the oxidant peroxynitrate. Except for NO_x^- , plasma biomarkers of endothelial function, including ET-1, were significantly decreased after 14 d of exposure, while 6-keto prostaglandin F₁ α (a stable product of prostacyclin) remained significantly decreased, dehydro-thromboxane B₂ (a stable product of thromboxane A₂) was significantly increased, and ET-1 was not affected after 28 d. The demonstration of an effect of ozone on these endpoints in vascular tissue supports a potential link between ozone and CVD. Thomson et al. (2005, 2006) investigated the independent and interactive effects of ozone (0.8 ppm) and EHC-93 particles (50 mg/m³) on lung ET-1, a potent vasoconstrictor associated with hypertension, myocardial ischemia, and arrhythmia. Exposure of rats to both ozone and EHC-93 resulted in an additive activation of preproET-1 mRNA in the lung (although plasma levels of ET-1 were not increased), coinciding with increased MMP-2, an enzyme that cleaves bigET-1 to ET-1[1-32]. The authors proposed that the oxidative stress and tissue injury produced by co-exposure and in excess of what was observed with ozone or particles alone may have inhibited translation of preproET-1 mRNA in the affected central acinus.

Two *in vitro* studies reported ozone-induced effects on blood cells and a potential connection between the macrophage response and atherosclerosis. Human peripheral blood MNCs were found to be sensitive to ozone-induced oxidation, particularly in serum with low antioxidant capacity (Larini and Bocci, 2005). Ozone exposure decreased IL-4 production, stimulated IFN- γ and TNF- α production, and increased markers of oxidative stress including protein thiol group content and lipid peroxidation. Products of cholesterol ozonolysis recently discovered in atherosclerotic arteries (atheronal-A and atheronal-B) were evaluated for their effects on monocyte/macrophage function *in vitro* (Takeuchi et al., 2006). The results indicated that atheronals could lead to the recruitment, entrapment, dysfunction, and destruction of macrophages and may represent a new association between inflammation, cholesterol oxidation, tissue macrophages and atherosclerosis. The processes by which atheronals are formed within atherosclerotic plaques are not well understood, but in light of recently reported *in vivo* formation of cholesterol oxidation products in the lungs of mice acutely exposed to ozone (Pulfer et al., 2005), the development of atheronals following chronic lung exposure to ozone cannot be ruled out.

Analysis of gene responses in various tissues of ozone-exposed animals may help elucidate the mechanisms underlying systemic effects. Last et al. (2005) employed global gene expression analysis of the livers of mice acutely exposed to 1 ppm ozone for 8 h/night for 3 nights in an attempt to elucidate the mechanisms underlying systemic responses to ozone. A very different pattern of gene expression was found in mice liver vs. a previous study of mice lung by the same investigators using equivalent exposure conditions. Most notably, NF- κ B signalling was not affected in the liver, although the expression of genes related to energy metabolism in the liver provided evidence of a suppressive response consistent with systemic cachexia. Selective P450 gene transcription was suppressed. The data were consistent with a role for IFN- γ as a signalling molecule between lung and liver but not with a role for TNF- α , as the investigators were unable to find circulating TNF- α in the blood plasma. In another study, exposure of hairless mice to 0.8 ppm ozone for 6 h/d for 6 d induced oxidative stress responses (e.g. induction of HO-1), activation of NF- κ B, and cell proliferation indicative of DNA replication and repair in both lung and cutaneous tissue (Valacchi et al., 2004).

15.3.4 Susceptibility

Susceptibility concerns physiological, age-related, genetic or other factors that augment the adverse health impacts of pollutants such as ozone. The 1999 Ozone SAD stated that age may be a factor in pulmonary sensitivity to ozone, with younger rats being more sensitive than older ones, and that species differences can factor in, with non-human primates being more responsive than rats. It was noted that one study found no difference in the response to ozone between rats with emphysema and normal healthy rats. By the time of the US EPA 2006 Ozone AQCD, studies had revealed that susceptibility to ozone was, in part, genetically determined. Experiments had shown that various strains of mice and rats differed with respect to their susceptibility to ozone-induced lung injury and inflammation, and genetic and molecular characterization studies had identified genetic loci that were at least partly responsible for both sensitivity and resistance in laboratory animals. Other factors found to potentially enhance the vulnerability to ozone-related effects included heightened exposures or activity patterns. Animal studies had provided evidence that exercise increased responsiveness to the pulmonary effects of ozone, in line with what had been found in controlled human exposure and epidemiologic studies. Pregnancy and lactation had been shown to increase the susceptibility of rats to acute ozone, but no clear effects of gender had been identified.

The effect of age on the response of rats to ozone was examined by Servais et al. (2005). Exposure to 0.5 ppm ozone for 7 d increased mitochondrial respiration, antioxidant enzyme activity, and oxidative DNA damage in aged (20-month-old) rats, and induced oxidative stress and DNA damage in immature (3-week-old) rats. By contrast, six-month-old adult rats were relatively resistant to the oxidative effects of ozone, supporting the notion that aged and immature animals are susceptible subgroups for these effects.

Oyarzun et al. (2005) used a bleomycin-induced pulmonary fibrosis rat model to study the effects of intermittent acute (4 h/d \times 5 d) and subchronic (4 h/d \times 60 d) exposures to 0.25 ppm ozone in chronically damaged lungs. Rats exposed for 5 d to ozone displayed an increase in the mean score of bleomycin-induced pulmonary inflammation and fibrosis ($p = 0.06$), and an increased frequency of bronchopneumonia ($p < 0.001$). However, bleomycin-induced lung damage did not differ from that in air-exposed control rats after 60 d of intermittent ozone exposure. Based on these results the authors suggested that the risk of further lung injury in a previously damaged lung is increased by short-term exposure to ozone, while intermittent subchronic ozone exposure may lead to the development of tolerance.

The interactive effects of malnutrition from a low protein diet and 30-d exposure to 0.5 ppm ozone on brain serotonin levels were examined in rats (Barragan-Mejia et al., 2002). Ozone decreased serotonin levels in the cerebellum of malnourished rats compared with those on a normal diet. The authors hypothesized that a lack of nutrient intake together with ozone exposure may cause oxidative stress, resulting in altered serotonergic metabolism and potential consequences for behaviour and CNS function.

The induction of hyperthyroidism by thyroxine exposure was reported to increase the acute inflammatory response of rats to 1–2 ppm ozone compared with normal control animals, as evidenced by increased lung permeability and neutrophil influx (Huffman et al., 2002, 2006a, 2006b). Mechanisms that may have contributed to the enhanced response of rats under hyperthyroid conditions include upregulation of cytokine production, specifically MIP-2 and MCP-1, and an increase in NF-κB binding. Ozone at 1 ppm was also shown to activate phospholipid surfactant production by type II cells in hyperthyroid rats but not in normal rats (Huffman et al., 2006b). These data suggest that abnormal thyroid hormone balance may affect susceptibility to the pulmonary effects of ozone.

As described in Section 15.3.1.3, intrapulmonary neuropeptides may play a role in the development of AHR following acute ozone exposure (Ren et al., 2004). The *in vitro* exposure of human nasal mucosa cells from allergic and non-allergic patients to ozone was found to increase neuropeptide content (neurokinin A and SP) in both cell cultures, but a significantly greater response occurred in cells from allergic vs. non-allergic patients (Schierhorn et al., 2002). These results support the hypothesis that neuropeptides contribute to elevating AHR in allergic patients exposed to ozone. Another *in vitro* study reported an ozone-induced increase in the permeability of human bronchial epithelial cells cultured from asthmatics, a response that was not detected in cells from non-asthmatics (Bayram et al., 2002).

In studies using high ozone exposure concentrations, obese mice (designated db/db, ob/ob, or Cpe^{fat}) were shown to have greater innate and ozone-induced AHR compared with normal wild-type mice following acute 3-h exposures to 2 ppm ozone (Rivera-Sanchez et al., 2004; Lu et al., 2006; Johnston RA et al., 2006). Changes in the breathing patterns of obese (db/db) mice resulted in a greater total ozone dose compared with wild-type mice. Ozone was shown to produce significantly greater lung resistance in obese (ob/ob) vs. wild-type mice, and pre-existing systemic inflammation in obese mice likely also contributed to their more pronounced responses (Rivera-Sanchez et al., 2004; Lu et al., 2006; Johnston RA et al., 2006).

15.3.5 Reproductive and Developmental Effects

Reproductive and developmental studies with experimental animals were not cited in the 1999 Ozone SAD. The US EPA 2006 Ozone AQCD noted that early studies employing pre- and postnatal exposure to ozone were performed with relatively high concentrations, and that teratogenic effects had not been observed with intermittent exposure levels between 0.44 and 1.97 ppm during any part of gestation. Continuous exposure in this range during mid-gestation was found to increase the resorption of embryos, and exposure during late gestation delayed some behavioural developments (e.g. righting and eye opening). There were no effects on neonatal mortality at exposure levels of up to 1.5 ppm ozone, whereas some transient effects on weight gain were observed at 0.6 ppm. The US EPA 2006 Ozone AQCD stated that more recent studies tended to confirm that prenatal exposures to ozone concentrations below 1 ppm did not cause major or widespread somatic or neurobehavioural effects in the offspring of laboratory animals. Infant rhesus monkeys episodically exposed to 0.5 ppm ozone over 5

months exhibited remodelling of the distal airways, abnormalities in the tracheal basement membrane, eosinophil accumulation in conducting airways, and decrements in airway innervation. Other postnatal ozone exposure studies reported a few subtle or borderline somatic and behavioural deficits.

The reproductive effects of 50-d subchronic exposure to 0.5 ppm ozone on 5-month-old male rats were examined by Jedlinska-Krawkowska et al. (2006a, 2006b). The sperm count in ozone-exposed rats was lower but not significantly different from controls. Ozone did not significantly affect the morphology and motility of spermatozoa; nor did it affect successful mating or the survival rate of newborns per litter measured one year postpartum (Jedlinska-Krawkowska et al., 2006b). A loss of germ cells and histopathological changes in the testes indicative of degenerative processes were found in male rats under the same ozone exposure scenario (Jedlinska-Krawkowska et al., 2006a). Administration of vitamin E during ozone exposure was observed to protect against histopathological changes, while high doses of vitamin C during exposure intensified damage to the testes.

Gestational exposure to ozone at 0.3 or 0.6 ppm was reported to alter the behaviour of adult male mice as measured by intermale agonistic patterns and social investigation (Santucci et al., 2006). Females were exposed to ozone from 30 d prior to the formation of breeding pairs until gestational d 17. Litters were fostered at birth to untreated dams and at adulthood male offspring underwent five successive daily encounters with a standard opponent of the same strain, sex, weight and age. Ozone-exposed mice showed a significant increase in freezing and defensive postures, a decrease in nose-sniffing behaviour, and a reduced aggressive behavioural profile. These behavioural changes were accompanied by changes in CNS levels of neurotrophins, including a decrease in hippocampal NGF and an increase in neurotrophic factor in the striatum. In another study, prenatal ozone exposure was reported to have adverse effects on the postnatal development of the cerebellum in rats (Romero-Velazquez et al., 2002). Exposure of pregnant dams to 1 ppm ozone throughout gestation decreased the total area and number of Purkinje cell neurons in the cerebella of male offspring compared with offspring from unexposed dams.

In an attempt to model the sensitivity of developing children to ozone, Fanucchi et al. (2006) examined the effects of 5 months of episodic ozone exposure on postnatal lung development in infant rhesus monkeys. Beginning at 30 days of age, monkeys were exposed for 11 episodes to 0.5 ppm ozone (6 to 8 h/d) for 5 d followed by a 9-d recovery period in fresh air. Ozone exposure reduced distal airway size and branching of the conducting airways, produced hyperplasia of the bronchiolar epithelium, and altered smooth muscle bundle orientation in terminal and respiratory bronchioles. The authors suggested that these results may contribute to explaining the observed decrements in the airway function of individuals raised in polluted areas of California's south coast air basin. The observed structural alterations could also explain the increased airway resistance reported in another study with infant rhesus monkeys using the same ozone exposure regimen. In this study, Joad et al. (2006) investigated the effects of 5-month episodic exposure to 0.5 ppm ozone and house dust mite allergen (HDMA) on the AHR of bronchi and respiratory bronchioles. HDMA alone produced AHR of the bronchi while HDMA plus ozone induced AHR in the respiratory bronchioles. Measures of pulmonary neuroendocrine cell volume per surface area of bronchi and eosinophil content were correlated with airway reactivity and appeared to play a role in the hyperresponsiveness of bronchi.

The influence of age and development on the respiratory responses of postnatal mice to acute ozone and LPS exposure were examined in studies using very high exposure levels. Critical time points during lung development were observed for responses to ozone or LPS inhalation, suggesting differences in the maturation of inflammatory and epithelial defence mechanisms. An abundance of mRNA for IL-6 was a sensitive indicator of postnatal lung growth and lung

sensitivity to ozone, as IL-6 mRNA was induced 18- to 20-fold by exposure to 2.5 ppm ozone in mice aged 10, 14, 28 and 56 days, but not in very young mice aged 2, 4 or 7 days (Johnston CJ et al., 2004). Acute exposure of 4-day-old mice to LPS prior to inhalation of 2.5 ppm ozone produced a synergistic inflammatory response as measured by increased IL-1 α and IL-1 β mRNA that was not observed with either LPS or ozone alone (Johnston CJ et al., 2005). A similar response was reported under the same exposure conditions for IL-6 mRNA production by mice aged 10 and 56 days. In contrast, inhalation of 0.5, 1 or 2.5 ppm ozone prior to LPS exposure inhibited the LPS-induced elevation of IL-1 α and IL-1 β mRNA in mice aged 4, 10 and 56 days. These data suggest that LPS exposure prior to ozone activates inflammatory cell recruitment resulting in the sensitization of mice to the effects of ozone, whereas ozone exposure prior to LPS may damage the airway epithelium and inhibit proinflammatory responses. Campos-Bedolla et al. (2002) reported that acute exposure of pregnant rats to the very high ozone concentration of 3 ppm for 1 h on d 5, 10 and 18 of gestation produced an increase in the maximum uterine contractile responses to oxytocin (d 5) and to ACh (d 5 and 10).

15.3.6 Carcinogenicity and Genotoxicity

The 1999 Ozone SAD noted that genotoxic and carcinogenic effects had been observed with long-term exposure to ozone, but the document did not go into details. The US EPA 2006 Ozone AQCD stated that the weight of evidence did not appear to support ambient ozone as a pulmonary carcinogen in laboratory animal models. It noted that lifetime and 2-year inhalation studies of ozone carcinogenicity from the National Toxicology Program (1994) were negative in male and female F344/N rats, while there was equivocal evidence of carcinogenic activity in male B6C3F1 mice based on increased incidences of alveolar/bronchiolar adenoma or carcinoma, and some evidence of carcinogenic activity in female B6C3F1 mice based on increased incidences of alveolar/bronchiolar adenoma or carcinoma at a high ozone concentration (1 ppm). These data were in general agreement with a study showing no significant increases in the incidence of lung tumours in B6C3F1 mice following 12 weeks of ozone exposure, and another study where ozone-related differences in lung tumour multiplicity or incidence after 9 months of exposure were not detected in the A/J mouse strain, known to have a high incidence of spontaneous pulmonary adenomas. However the exposure durations in these latter studies were likely too limited to detect effects. The US EPA 2006 Ozone AQCD stated that recently published *in vivo* studies had found increased DNA strand breaks in respiratory cells from guinea pigs and mice but only with high exposure levels, while *in vitro* studies were difficult to interpret due to very high exposure levels and culture systems that allowed potential artefact formation. Overall these studies were found to be inconclusive.

New *in vivo* and *in vitro* studies on the genotoxic potential of ozone have reported DNA strand breaks, increased mutation frequency, and adduct formation. Genotoxicity was analyzed in tracheobronchial epithelial (TE) cells isolated from Dunkin-Hartley guinea pigs following 72-h *in vivo* exposure to ozone at 0.45 or 1 ppm (Ferng, 2002). The occurrence of DNA single strand breaks in TE cells was a linear function of ozone concentration, but was only significantly increased in the 1 ppm ozone exposure group. Kim et al. (2004) investigated the genotoxic effects of chronic exposure to 0.5 ppm ozone, as well as the effects of the tobacco-specific nitrosamine NNK, the plasticizer and weak estrogen receptor agonist dibutyl phthalate, and combinations of these toxicants in isolated splenic T-cells of male and female B6C3F1 mice following *in vivo* exposure for 6 h/d, 5 d/week for 32 and 52 weeks. Ozone alone significantly increased the mutation frequency of splenic T-cells as measured by the hypoxanthine guanine

phosphoribosyl transferase (hprt) assay, while additive interactions were observed following exposure to ozone plus NNK or dibutyl phthalate.

Several new *in vitro* studies were identified in the literature. DNA damage was evaluated in human A549 cells as indicated by single strand breaks and adduct formation following exposure to ozone with or without antioxidant vitamins or the formamidopyrimidine glycosylase (Fpg) repair enzyme, used to detect oxidative damage (Cheng et al., 2003). Ozone was found to induce DNA single-strand breaks and DNA adduct formation (8-oxoguanine); strand breaks were observed in the presence of Fpg, while pretreatment with vitamins C or E reduced DNA adduct formation. In another study, exposure of human leukocytes to ozone resulted in a dose-dependent increase in DNA strand breaks that was comparable to DNA damage induced by H₂O₂, used as a positive control (Diaz-Llera et al., 2002). The ozone-induced DNA damage may have resulted from H₂O₂ formation following the reaction of ozone with unsaturated fatty acids in cell membranes, as pre-incubation of leukocytes with catalase prevented genotoxicity. Ito et al. (2005c) assessed the genotoxicity of ozone in solution with DNA via a DNA sequencing technique using radiolabelled DNA fragments. They reported that ozone-induced DNA backbone cleavages likely occurred via hydroxyl radical formation, while ozone itself produced DNA base modifications.

15.3.7 Effects of Chemical Mixtures Containing Ozone

In a discussion of research on chemical mixtures containing ozone, the 1999 Ozone SAD noted that a study of the effects of ozone and H₂SO₄ alone and in combination revealed inflammatory effects that were additive but not clearly synergistic. A study of ozone and cigarette smoke in guinea pigs found that inhalation of both irritants increased airway responsiveness and permeability, while exposure to each separately at the same concentration produced no effect. The US EPA 2006 Ozone AQCD stated that it was difficult to summarize the role that ozone plays in exposure responses to binary mixtures, and even harder to determine its role in responses to multi-component, complex atmospheres. The database generally showed that ozone produced more significant biological responses as a component of a mixture than when inhaled alone. Interactive effects with ozone had been observed with NO₂, endotoxin, tobacco smoke, formaldehyde, and pollutant mixtures containing acid aerosols or other particle types. Antagonism was noted in a few studies. However, the document noted that any description of interaction was valid only for the specific conditions of the study in question and could not be generalized to all conditions of exposure to a particular chemical mixture due to the complexities involved. Most studies had shown that interactions occurred only at higher than ambient concentrations with acute exposure.

The results of some recent toxicological studies support earlier assertions that pollutant interactions with ozone can produce enhanced toxicity in the lung, although several studies did not observe an exacerbation of inflammatory effects, possibly due to acute lung injury or adaptation following chronic exposure. Kleinman and Phalen (2006) examined the acute effects of inhaled ozone at 0.3 or 0.6 ppm alone or in mixtures with 0.3 µm H₂SO₄ aerosols at 0.5 or 1 mg/m³ and found that pollutant interaction was dependent on the inflammatory endpoint measured in rats. Addition of H₂SO₄ to ozone-containing atmospheres resulted in significant reductions to ozone-induced inflammatory responses that were H₂SO₄ concentration-dependent. Epithelial cell injury was significantly increased by ozone but not H₂SO₄ when administered alone compared with inhalation of purified air. H₂SO₄ did not decrease ozone-induced epithelial injury in the trachea or the lung, but did reduce this response in the nose. H₂SO₄ alone and in combination with ozone also depressed some functions of innate immunity. Pulmonary injury and decrements in immunological function were evaluated in aged

rats (22–24 months old) exposed nose-only for 4 h/d, 3 d/week for 4 weeks to 0.2 ppm ozone alone or in mixtures with a low or high concentration of fine particles (Kleinman et al., 2003). The particles used were EC and ammonium bisulphate with MMADs of 0.3 μm , at concentrations of 50 $\mu\text{g}/\text{m}^3$ and 70 $\mu\text{g}/\text{m}^3$ in the low concentration particle mixture, and 100 $\mu\text{g}/\text{m}^3$ and 140 $\mu\text{g}/\text{m}^3$ in the high concentration particle mixture, respectively. Exposure to the particle and ozone mixtures produced a range of significant effects. For some responses, including enhanced lung cell replication, increased epithelial permeability and reduced macrophage respiratory burst activity, responses were lower rather than greater with the high-concentration particle mixture. Exposure to ozone alone at 0.2 ppm did not result in significant changes to any of the measured endpoints. The authors rejected experimental bias as an explanation for the plateaued or attenuated responses to the mixtures; they suggested, however, that these results may reflect the induction of repair (e.g. cell turnover) or lung defence (respiratory burst) at the low dose, with tissue injury blocking these responses at the high particle concentration. Alternatively the time course of injury and peak response may have been altered.

Cassee et al. (2005) conducted a study in which rat lungs were compromised by acute exposure to 0.8 ppm ozone followed by a series of 1-d inhalation exposures to CAPs from various locations in the Netherlands. CAPs were 0.15–2.5 μm in size and their time-integrated mass concentrations ranged from 270 to 3720 $\mu\text{g}/\text{m}^3$. Exposure to ozone alone decreased GSH content in BALF, produced pulmonary inflammation and cell proliferation, and increased lung permeability. Subsequent CAPs exposure contributed little to ozone-induced inflammation but appeared to increase ozone-induced lung permeability.

The independent and interactive effects of 0.4 or 0.8 ppm ozone and EHC-93 urban air particles at 5 or 50 mg/m^3 on the lung endothelin system were investigated in rats (Thomson et al., 2005). Combined but not individual exposure to ozone and EHC-93 resulted in an immediate increase in MMP-2 in the rat alveoli, consistent with the enhanced septal remodelling and thickening previously demonstrated with co-exposure to these pollutants. Exposure to ozone plus EHC-93 resulted in activation of lung endothelin system genes but did not increase plasma levels of ET-1. Oxidative stress and tissue injury produced from co-exposures were in excess of what was observed with ozone or EHC-93 alone, which may have inhibited translation of preproET-1 mRNA in the affected central acinus. A further study investigated the effects of ozone and EHC-93 on expression of endothelins (ET-1_[1-21], ET-2_[1-21], and ET-3_[1-21]) in rats at the peptide and gene expression levels. Co-exposure to ozone and EHC-93 did not alter plasma levels of ET-1 or ET-3, despite increased endothelin gene expression in the lungs (Thomson et al., 2006).

Combined exposure to 0.4 ppm ozone and urban particles (EHC-93, 4800 $\mu\text{g}/\text{m}^3$) for 12 weeks was not found to cause inflammation or lung injury in wild-type mice; nor did it exacerbate pre-existing lung inflammation and injury in mice over-expressing TNF- α (TNF mice), possibly due to the adaptation of these mice to chronic inflammation (Kumarathasan et al., 2005). However, the pollutants exacerbated the rate of protein nitration reactions in the lungs of TNF mice (as revealed by the high ratio of 3-nitrotyrosine to L-DOPA following exposure) and also increased serum creatine kinase-MM isoform. The pollutant-related nitration in the lungs of TNF mice may indicate basic differences in free radical generation and scavenging in inflamed lungs in response to pollutants. The effects of ozone or particles alone were not determined in this study.

Synergistic effects on oxylipid formation and the expression of cytokines attributed to airway remodelling were reported in rats exposed to 0.8 ppm ozone for 8 h/d for 90 d followed by injection with 1-nitronaphthalene (1-NN), a component of DEPs found at low concentrations in ambient air (Schmelzer et al., 2006). Under the same exposure conditions another study reported that the pattern of 1-NN-induced protein adduct formation in the rat airway epithelium

was altered, indicating that pre-exposure to ozone may exacerbate 1-NN toxicity by affecting antioxidant defence and regulation of immune responses (Wheelock et al., 2005). However, the relevance of these studies is limited by the use of injection as the route of exposure for 1-NN rather than inhalation. Kafoury and Kelley (2005) conducted an *in vitro* study to determine the effect of ozone plus DEP on IL-8 gene expression in human airway epithelial A549 cells. Co-exposure of cell cultures to ozone plus DEP enhanced gene expression of IL-8 beyond that observed with DEP alone, which was attributed to an ozone-induced increase in the activity of the transcription factors NF- κ B and NF-IL-6.

Two recent studies looked at combined exposure to very high levels of ozone with other substances. Wilkins et al. (2003) reported upper airway irritation measured as respiratory rate reduction in mice following exposures to reaction mixtures of ozone at very high concentrations (1, 2, 3.5 and 4 ppm) plus terpenes (50 ppm limonene or 500 ppm isoprene). Terpenes are VOCs that are commonly found indoors. It was determined that the irritant potencies for terpene/ozone oxidation products, which include aldehydes, were comparable to pure irritants such as formaldehyde and acrolein. In another study, an additive AHR response to OVA was observed in OVA-sensitized mice as a result of combined exposure to 2 ppm ozone and a DEP aerosol at 2 mg/ μ L (Jang et al., 2005a). Combined pollutant inhalation and OVA challenge increased total cell number and the proportion of eosinophils and neutrophils in BALF and decreased IFN- γ levels compared with unexposed sensitized mice or OVA-challenged mice exposed to ozone only.

15.3.8 Summary and Considerations: Animal Toxicology

Recent studies substantiate the characterization of ozone-induced lung injury and inflammatory responses detailed in the 1999 Ozone SAD and US EPA 2006 Ozone AQCD. The mechanisms leading from ozone exposure to lung injury and inflammation have been relatively well characterized. The interaction of ozone with the lung lining initiates a reactive cascade, resulting in free radical generation and oxygenated biomolecules that penetrate into cells and mediate the biological effects of ozone, which can include epithelial injury, increased airway permeability and inflammation in the upper and lower airways. Biochemical changes such as depletion of antioxidants and damage to polyunsaturated fatty acids and proteins accompany these effects. New studies, some of which used genetic knock-out mice and gene expression profile analysis, have added to this relatively well-defined picture to further elucidate the roles of inflammatory mediators (e.g. chemokines, superoxide anion, NO), transcription factors (e.g. NF- κ B), SPs and macrophages in the response to ozone. Recent studies provide further evidence for the formation of specific lipid oxidation products following the reaction of ozone with target molecules in the lipid-rich pulmonary ELF. *In vivo* and *in vitro* work has demonstrated the ozone-induced modulation of antioxidant enzyme activities and the ability of endogenous and exogenous antioxidants to protect against ozone-induced injury, and also support a protective role for SPs. There were conflicting results regarding the involvement of inducible NOS2 in lung injury and inflammation, possibly dependent on exposure concentration and duration. Previous acute *in vivo* studies reported epithelial injury and inflammation at ozone levels as low as 0.1 ppm, and no evidence for effects below this level has been identified.

As interest in the relationship between air pollution and asthma has grown, studies on the effects of ozone on pulmonary function have moved away from traditional endpoints such as lung volume and breathing frequency discussed in previous assessments to measures of increased airway sensitivity and experimental allergy models. Pulmonary endpoints such as FVC were briefly discussed in the 1999 Ozone SAD, along with increased airway responsiveness. The US EPA 2006 Ozone AQCD noted that animal studies had shown that

acute ozone exposures could affect breathing compliance and resistance (~1 ppm), decrease lung volume (0.5 ppm), and cause rapid shallow breathing. Ozone had been found to increase AHR to nonspecific bronchoconstrictive agents in various animal models following acute exposures to 0.5–1 ppm, with inflammation not a prerequisite for this response. The factors contributing to or controlling ozone-induced AHR have been investigated in recent literature. Studies suggest that TLR4 may play a role in ozone-induced heightened airway responsiveness, and that CXCR, a receptor for neutrophil chemotactic factors, may be involved in sustaining the response. A large number of recent studies used very high ozone exposure levels (2–3 ppm), and so the applicability of their results is uncertain. These studies suggest that parasympathetic nerves, NO generation in the airways, altered calcium mobilization in airway smooth muscle, and increased permeability of the airway mucosa could play a role in AHR induction. The link between AHR and inflammation is still not entirely clear, as some evidence points to a role for inflammatory mediators (e.g. IL-1 β) but the database is not fully consistent.

The US EPA 2006 Ozone AQCD discussed studies showing the ability of ozone to augment antigen-induced AHR in sensitized laboratory animals, consistent with the ozone-induced exacerbation of AHR reported in atopic humans with asthma. It was noted that the results of animal studies were difficult to extrapolate because of interindividual and interspecies differences in responsiveness to bronchoprovocation, and the possible adaptation of airway responsiveness with long-term, repeated ozone exposures. Additional support for the ozone-induced enhancement of responses to allergens in sensitized animals is found in recent literature. A synergistic interaction between acute ozone exposure and ovalbumin in evoking increased airway reactivity and immunologic responses has been demonstrated in sensitized rats, mice and guinea pigs. Equivocal results have been reported for longer-term ozone exposures: sensitized guinea pigs and C57BL/6 mice demonstrated exacerbated pulmonary and inflammatory effects similar to those observed with acute exposure, while sensitized BALB/c mice displayed an attenuation of these effects during subchronic exposure, as well as decreased AHR and inflammatory responses to antigen associated with airway remodelling. A study with guinea pigs reported benchmark concentrations for ozone calculated at the 95% lower limit, corresponding to an additional 10% risk of enhancement of nasal allergy-like symptoms ranging from 0.06 ppm for sneezing responses to 0.14 ppm for eosinophil infiltration of the epithelium and subepithelium.

Acute ozone exposure has been shown to increase the susceptibility of laboratory animals to infectious diseases due to modulation of lung host defences. Research described in the 1999 Ozone SAD and US EPA 2006 Ozone AQCD demonstrated increased mortality and morbidity, decreased lung clearance, increased bacterial growth, and increased severity of infection at exposure levels of 0.1–1 ppm ozone for up to a week. Aside from one study with mice suggesting that ozone could impair both natural killer cell activity and the proliferation potential of splenic T- cells to a specific antigen stimulus, and several *in vitro* studies examining the modification of AM function by ozone exposure, no new published research was identified on host defence and the effects of ozone on resistance to infection.

Research on neurological endpoints was not identified in the 1999 Ozone SAD. By the time of the US EPA 2006 Ozone AQCD, neurobehavioural effects had been reported in a number of studies over a concentration range of 0.2–1 ppm ozone. These effects included short- and long-term memory deficits and decreased motor activity and exploratory behaviour, associated with increases in reactive oxygen/nitrogen species and altered neurotransmitter levels. Morphological changes in several brain regions and altered EEG patterns during sleep had also been reported. However, the underlying mechanisms of these effects were little understood. The body of evidence for ozone-induced effects on the nervous system has expanded. Experimental animal research has demonstrated neuropathological and behavioural changes

following ozone inhalation; however, information on the biochemical and molecular mechanisms behind these responses remains limited. Recently reported CNS effects include dopaminergic neuron dysfunction; damaged or reduced density of neurons in the substantia nigra and striatum; lipid peroxidation in the cortex, striatum, midbrain, thalamus, hypothalamus and pons; alterations in brain catecholamine levels; and morphological effects on granule cells of the olfactory bulb. Some of these responses were accompanied by evidence of oxidative stress, and its alleviation or prevention by antioxidant administration supports a role for a ROS-related mechanism. In recent identified literature the lowest ozone exposure level reported to cause CNS effects was 0.25 ppm. The ability of some regions of the CNS to better tolerate ozone exposure was attributed to differential distribution of pro-oxidant molecules and antioxidant enzymes. Effects on postnatal development of the rat cerebellum and behavioural modifications in adult male rats were observed following gestational exposure to ozone. A number of recent studies reported acute effects on sleep–wake homeostasis in rats, including decreased REM sleep and increased slow wave sleep, effects that were associated with lipid peroxidation and the production of inflammatory mediators as well as disruptions in neurotransmitter activity.

The 1999 Ozone SAD mentioned several cardiovascular effects of ozone reported in rodents, including decreased heart rate and increased frequency of arrhythmia, and the US EPA 2006 Ozone AQCD noted that a number of experimental animal studies had demonstrated an ozone-induced hypothermic response involving decreased heart rate and mean arterial pressure at exposure levels in the range of 0.1–0.5 ppm. Recent research on cardiovascular and other systemic responses to ozone has been minimal. There is new *in vivo* evidence of ozone-induced endothelial dysfunction and peroxynitrite formation in rats, and *in vitro* evidence of effects on blood cells and a potential connection between the macrophage response to ozone and atherosclerosis. Other systemic responses to ozone demonstrated in recent studies include oxidative stress and cell proliferation in mouse cutaneous tissue, and down-regulation of different families of mRNAs in the livers of mice, including genes related to metabolism. These studies, along with those on CNS effects, indicate a systemic response to ozone evident beyond the pulmonary system, but the underlying mechanisms are not well understood.

Susceptibility factors identified in previous assessments include age and species differences (1999 Ozone SAD), heightened activity patterns, genetic differences, and pregnancy/lactation (US EPA 2006 Ozone AQCD). New studies provide information on potentially important factors including age, malnutrition, hyperthyroidism, pulmonary fibrosis and obesity. One recent study found that immature and aged rats were more sensitive to ozone-induced oxidative stress than adult rats. Malnutrition could influence susceptibility to ozone exposure, as suggested by a study in which serotonin in the cerebellum of malnourished rats was decreased following ozone exposure compared with rats on a normal diet. A role for thyroid hormones in modulating the inflammatory response of the lung to ozone was suggested by work that demonstrated an increased sensitivity of hyperthyroid rats to ozone compared with normal control animals. Several studies using a high exposure level (2 ppm ozone) reported that obesity produced greater innate and ozone-induced airway reactivity responses. Recent *in vitro* data suggest that certain biochemical and cellular differences related to neuropeptides and epithelial cell permeability may play a role in the heightened susceptibility of allergic and asthmatic subjects to ozone in comparison with normal healthy subjects. Although there is new information on different aspects of susceptibility, it is generally in areas that have not been previously studied and so does not build upon work cited in previous assessments.

Reproductive and developmental effects have received limited attention. The US EPA 2006 Ozone AQCD noted that continuous ozone exposure in the range of 0.44–1.97 ppm during mid-gestation increased embryo resorption, while exposure during late gestation delayed some behavioural development. More recent studies tended to confirm that prenatal exposures below

1 ppm did not cause major or widespread somatic or neurobehavioural effects in the offspring of laboratory animals. However, episodic exposure of infant rhesus monkeys to 0.5 ppm ozone over 5 months resulted in the remodelling of distal airways among other pulmonary developmental effects. Recent literature provides new information on the potential reproductive and development effects of ozone exposure. A possible link between oxidative stress and adverse effects on germ cells and histopathological changes in the testes was found in subchronically exposed rats. In contrast to previous assessments, gestational exposure to ozone levels below 1 ppm was linked in one recent study to altered behaviour in the adult offspring of exposed mice (0.3 or 0.6 ppm), with effects indicative of a reduced aggressive behavioural profile and accompanied by changes in CNS levels of neurotrophins. Another study reported cellular changes in the cerebellum of male rat offspring following prenatal exposure to 1 ppm ozone. Subchronic ozone exposure was observed to affect postnatal lung development in infant rhesus monkeys, causing structural alterations such as reduced branching of the conducting airways. Although the effects occurred at the relatively high ozone exposure level of 0.5 ppm, these results support studies discussed in the US EPA 2006 Ozone AQCD in which chronic ozone exposure of infant monkeys sensitized to HDMA resulted in altered development of the tracheal basement membrane, increased allergic and airway remodelling responses, and altered neural development in the airway epithelium. Together these data suggest that ozone may compromise postnatal morphogenesis of the tracheobronchial airways.

Based on information available at the time, the US EPA 2006 Ozone AQCD stated that the weight of evidence did not appear to support ambient ozone as a pulmonary carcinogen in laboratory animal models. There was some evidence of both *in vivo* and *in vitro* genotoxicity, but overall these studies were found to be inconclusive. No new studies of ozone carcinogenicity and only a few new genotoxicity studies were identified. Chronic exposure of mice to 0.5 ppm ozone was found to increase the mutation frequency of splenic T-cells. DNA strand breaks were reported in the tracheobronchial epithelial cells of guinea pigs following short-term *in vivo* exposure to 1 ppm ozone, and in A549 cells and leukocytes *in vitro*. Ozone-induced DNA adduct formation was also observed in A549 cells. A role for oxidative damage in the genotoxic effects of ozone is supported by data from two *in vitro* studies in which pre-treatment with antioxidants reduced genotoxicity. These data constitute evidence that ozone may be genotoxic in laboratory animals, though only with high exposure levels. Overall the state of knowledge from previous assessments has not dramatically changed and the database remains inconclusive.

The 1999 Ozone SAD noted that ozone and H₂SO₄ had been found to produce additive but not clearly synergistic inflammatory effects, and another study had found that inhalation of ozone and cigarette smoke increased airway responsiveness and permeability in guinea pigs, while exposure to each separately at the same concentration produced no effect. The US EPA 2006 Ozone AQCD stated that interactive effects with ozone had been observed with NO₂, endotoxin, tobacco smoke, formaldehyde, and pollutant mixtures containing acid aerosols or other particle types, with antagonism noted in a few studies, but also pointed out that any description of interaction was valid only for the specific conditions of the study in question and could not be generalized to all conditions of exposure to a particular chemical mixture. Although research examining the health effects of chemical mixtures containing ozone remains limited, some recent studies support the findings of past assessments indicating that combined exposures to ozone and other pollutants can enhance toxic responses in the lung. Several studies reported that co-exposures to ozone and urban particles produced oxidative stress and tissue injury in rats in excess of what was observed with either pollutant alone, though it must be noted that other studies have found no evidence of interactive effects.

15.4 Controlled Human Exposure Studies

Controlled human exposure studies (sometimes referred to as clinical studies) are a useful complement to epidemiological studies in that exposure to an individual pollutant or pollutant mixture can be carefully controlled in a well-defined group of subjects, exposure–response relationships can be characterized, and the influence of environmental variables such as exercise, humidity or temperature can be examined. However, these types of studies are generally limited to examining short-term, mild, reversible alterations in health endpoints, typically in individuals who may not represent those at most risk (WHO, 2003). While potentially susceptible populations may be directly studied, those with more severe pre-existing disease, and hence most likely to be affected by air pollutants, are usually excluded from studies for ethical reasons. Another drawback is that exposure is typically limited to single-pollutant exposure or to a very limited pollutant mix, which never replicates the complex mixture to which populations are actually exposed. Aerosol concentrators have been developed to allow “real world” inhalation exposure to CAPs. Limited controlled human exposure studies have examined simultaneous exposure to CAPs and ozone, while most studies examined ozone alone or ozone plus a single pollutant. Finally, whether or not transient responses in such studies predict more chronic and persistent effects is unknown.

Included in this section are studies of subjects exposed (at rest or during intermittent periods of exercise) for 1–8 h to ozone concentrations of 0.04–0.4 ppm.

15.4.1 Summary of Previous Assessments

The 1999 Ozone SAD contained information from the published literature current to April 1997. It was clearly recognized that increased ventilation was associated with increased responses to ozone (e.g. effective dose: minute ventilation \times ozone concentration \times duration); i.e. the acute response to ozone was exacerbated by exercise. It was reported that there was no apparent threshold for ozone-related declines in spirometry. Acute exposures of 4 h or less to concentrations as low as 0.12 ppm were reported to cause lung function decrements and increased bronchial responsiveness, but there were no reports of inflammatory response. Effects were observed at lower concentrations after prolonged exposures (6–8 h exposure to 0.08–0.12 ppm), including increased bronchial responsiveness, increased inflammation and decreased spirometry. Correlations were not observed between spirometric changes and either airway resistance, bronchial responsiveness or inflammatory responses. In addition, ozone responders as per spirometry were not necessarily responders with respect to inflammatory endpoints. It was suggested that FEV₁ was a relatively sensitive marker for ozone-induced effects. Data from repeated exposure studies typically showed that responses were enhanced on the first or second day of exposure and were attenuated after exposure on subsequent days. This attenuation was most pronounced/rapid for spirometric and symptom responses and somewhat less for bronchial responsiveness, while only some markers of cell injury showed adaptation, implying ongoing tissue damage during repeated exposures.

Asthmatics were recognized as being susceptible to the health effects associated with exposure to air pollution. They did not exhibit substantially stronger pulmonary function responses than healthy subjects following acute exposure to ozone, but they did exhibit higher airway cellular responses and higher ozone-modulated responsiveness to allergens. With prolonged exposure to ozone, asthmatics experienced higher pulmonary function and symptom responses than healthy subjects. There was evidence from one study of COPD subjects and one study of

subjects with allergic rhinitis to suggest that these groups may be at increased risk of ozone-induced decrements in lung function. Although there was no clear evidence that age was a modifying factor of pulmonary response or inflammatory endpoints, adolescents appeared more sensitive to changes in lung function than adults, and older adults were less responsive than younger adults. Exercising individuals were identified as a potentially susceptible group after research indicated that peak ozone had a greater effect on FEV₁ compared with a constant dose over the same duration, since exertion is known to increase the biological response to ozone, and exercising people could potentially be exposed during periods of peak ozone. Studies of co-exposures with other pollutants indicated some synergism between ozone and SO₂ in inducing bronchial hyperreactivity, and an enhancement of ozone-induced spirometric changes by NO₂ or sulphuric acid.

Much of the literature reviewed in the US EPA 2006 Ozone AQCD focused on the mechanisms of inflammatory responses to ozone and cellular responses to injury, with the evidence presented suggesting a role for neural/nociceptive mechanisms. Studies confirmed previous evidence that ozone is associated almost entirely with respiratory and inflammatory endpoints, rather than with extrapulmonary effects. Humans with controlled exposure to near-ambient levels of ozone exhibited decreased inspiratory capacity, mild bronchoconstriction, shallow rapid breathing during exercise, decreased lung function, and increases in symptoms of respiratory discomfort, AHR, inflammation, immune system activation and epithelial injury. In resting healthy subjects, the lowest observed adverse effect level for decrements in lung function was identified as 0.5 ppm. However, declines in lung function were reported at concentrations as low as 0.08 ppm in healthy adults if minute ventilation or duration were sufficiently great. Intersubject variability was noted even at this low concentration, making it difficult to suggest that a threshold would exist in a heterogeneous population. Limited studies suggested that inflammatory responses occurred at concentrations that did not result in pulmonary function changes. There was consistent evidence that changes in pulmonary function were not related to cellular and biochemical changes or inflammatory responses.

There was clear evidence of a large degree of interindividual variability in pulmonary responses to ozone, but only minimal intraindividual variation over a period of months. At high, but not low, concentrations, enhanced responses on the second day of repeated exposure were observed. After repeated daily exposure over several days, attenuation of effects (i.e. observation of reduced response), more pronounced for respiratory and symptomatic endpoints, was observed, with residual effects cleared by 24 h post-exposure. Less attenuation of hyperresponsiveness was observed, and while some inflammatory markers showed attenuation, markers of lung injury and permeability did not; effects persisted up to 48 h. Lack of attenuation may indicate ongoing tissue damage with repeated exposure to ozone.

Several potential factors that may affect responsiveness to ozone were reported. It was shown that the exposure profile of ozone impacted the degree of health effects observed with triangular exposures (simulating ambient ozone levels that vary diurnally, peaking mid-afternoon with lower concentrations in the morning and evening), producing greater effects than square wave exposures of the same total concentration; this suggested that ozone concentration is more important than total inhaled ozone dose. In healthy adults ozone-related spirometric changes were not dependent on gender, race, body surface area, height, lung size or baseline FVC. However, age was strongly associated with spirometric responses, which were similar in children and adults but declined with age beginning in early adulthood. Symptoms also declined with age in adults, and fewer symptoms were also reported in children. There was evidence that dietary antioxidants attenuated effects on spirometry and bronchial hyperresponsiveness but not symptoms or inflammation. Study results suggested that genetic polymorphisms for antioxidant enzymes and inflammatory genes (GSTM1, NQO1, and *Tnf-α*) modulated pulmonary function

and inflammatory responses, which may confer susceptibility on some subjects. There was only weak evidence to support the hypothesis that exposure to mixtures containing ozone elicited stronger effects than exposure to ozone alone.

Data continued to suggest that asthmatics were more susceptible to the health effects associated with exposure to ozone. In acute, but less so in repeated measures studies, declines in lung function were at least equal to, if not slightly more pronounced, in asthmatics compared with healthy subjects. Attenuation of the effects of ozone on spirometric values following repeated exposure was observed in asthmatic subjects, but AHR increased with repeated exposure to ozone in subjects with allergic airway disease. Subjects with rhinitis had an increased immediate response to allergens after exposure to ozone compared with healthy subjects. There was very little evidence to suggest that ozone-induced changes in spirometry or cardiovascular endpoints were more pronounced in subjects with CVD or COPD, which may have been related to the greater age of these subjects.

15.4.2 Respiratory Effects

15.4.2.1 Acute Exposure

A limited number of new studies of respiratory effects in humans following acute (1- to 3-h) controlled exposures to ozone have been published; some of these have focused on less traditional measures of pulmonary response.

The specific spirometric measures such as FEV₁ and FVC depend on a combination of tissue mechanics and gas dynamics but provide little insight into pulmonary gas transport. Some research has explored the utility of the CO₂ expirogram, a plot of the concentration of expired CO₂ versus expired volume, as a tool for examining the effects of ozone on regions of the respiratory tract. Taylor et al. (2006) examined the relationship between ozone-induced decrements in lung function and CO₂ expirogram parameters in 47 subjects exposed to 0.25 ppm for 1 h with intermittent exercise. Ozone-induced reduction in the percentage change in FEV₁ was correlated with percentage change in V_D (anatomical dead space, an indicator of the volume of the conducting airways), but not A_P (a CO₂ expirogram parameter that measures the gas transport process as the peripheral cross-sectional area from the alveolar plateau). This suggested that the results for both FEV₁ and V_D reflected effects of ozone in the conducting airways, while changes in A_P were related to ozone-induced effects in the more distal lungs. The use of A_P is a novel marker of functional changes in the peripheral lungs, but the physiological significance of changes in A_P has not been validated (Health Effects Institute statement, *in* Ultmann et al., 2004).

In an earlier study (Reeser et al., 2005), 1-h inhalation of 0.25 ppm ozone by 60 healthy adults with continuous exercise resulted in significant decrements in %ΔFEV₁, %ΔA_P, and %ΔV_D. Individual values of ozone uptake efficiency ranged from 0.70 to 0.98, and were significantly higher in men than in women. However, contrary to the study hypothesis, ozone uptake was a poor predictor of intersubject variation in the response of conducting airways (i.e. change in FEV₁ or in V_D). Ozone uptake was, however, significantly correlated with percentage change in A_P at 10 min post-exposure, which the authors suggested was an indication of pulmonary response in the distal airspaces.

In contrast to the results of studies reviewed in the US EPA 2006 Ozone AQCD, in a recent study antioxidant supplementation did not protect against pulmonary responses observed after exposure to ozone. Ozone-sensitive, but otherwise healthy, subjects (n = 14) were chosen as those with the greatest decrements in FEV₁ after a screening visit exposure to 0.2 ppm ozone for 2 h with moderate exercise. Subjects completed three 2-h chamber exposures, separated by

at least 3 weeks, to (a) filtered air, (b) 0.2 ppm ozone preceded by 7 d of supplementation with 500 mg vitamin C and 100 mg vitamin E, and (c) 0.2 ppm ozone preceded by 7 d of placebo supplementation. A significant decrease in FEV₁ was observed after both placebo and vitamin treatments, but the difference in the percentage decrease between the two groups was not significant. The small sample size may have limited the statistical power to detect small differences (Mudway et al., 2006).

Morrison et al. (2006) observed no significant changes in spirometry or lung damage after healthy subjects were exposed to 0.1 or 0.4 ppm ozone for 1 h via face mask, with intermittent exercise. FEV₁ and FVC were decreased, but were not statistically significant, perhaps as a result of the very small sample size (five to seven per group).

Molhave et al. (2005) investigated interactions between ozone and office dust in atopic individuals (four males and four females). Subjects were exposed in a chamber to ozone alone (0.3 ppm), dust alone (75 µg/m³ (0.0375 ppm)) or combined exposure to ozone and dust for 3 h. Exposures, conducted in random order, were separated by 1 week. Compared with ozone alone or dust alone, combined exposure was associated with a greater decrease in PEF (significantly greater than ozone-only exposure) and significantly increased discomfort (eyes, nose and throat). No significant effects were associated with exposures to ozone or dust alone compared with pre-exposure. The small number of subjects and the omission of a clean air exposure reduce confidence that the observed changes are due to exposure. Low statistical power may be responsible for the lack of significant findings after exposure to ozone alone.

Chen et al. (2004) investigated whether exposure to ozone enhanced early and late responses to inhaled HDMA in sensitized asthmatic subjects. Thirteen males and one female subject were randomly exposed to 0.2 ppm ozone or filtered air for 1 h while exercising, followed by an allergen challenge. Exposures were separated by at least 4 weeks. Lung function measurements were made before and after each exposure and hourly for 5 h after allergen challenge. There was some evidence of an association between sensitivity to ozone as measured by acute lung function responses and increased sensitivity to HDMA after ozone exposure. Overall, no change in PC₁₅ (concentration of *Dermatophygoidea farinae* causing a 15% decrease in FEV₁ from the post-saline solution baseline) was observed, but PC₁₅ values tended to be lower in subjects with the greatest ozone-related declines in FEV₁. Declines in FEV₁ and FVC and increases in specific airway resistance were similar after ozone and air exposures; however, more lower respiratory symptoms were reported after exposure to ozone. A non-significant trend towards decreased PC₁₅ after ozone exposure compared with air exposure was observed. In a further analysis, it was suggested that ozone sensitivity (greatest declines in FEV₁) may predict increased allergen sensitivity (lower PC₁₅ values) after exposure to ozone; however, changes in spirometric endpoints in the seven of nine individuals with lower PC₁₅ after ozone were not significant (perhaps a result of the small sample size).

15.4.2.2 Prolonged and Repeated Exposures

A number of studies of the respiratory effects of prolonged (4- to 8-h) and/or repeated exposure to ozone were published in the review period, and are presented below.

A study by Adams (2006a) assessed pulmonary responses and symptoms of breathing discomfort among 30 male and female healthy young adults before, during, and after exposure to filtered air or 0.04–0.08 ppm square wave or triangular profiles of ozone for 6.6 h with intermittent exercise. This study was considered key in the US EPA 2006 Ozone AQCD (discussed above). The 6.6-h exposure in the chamber included six 1-h segments involving 50 min of exercise with 10 min of rest, as well as a 35-min lunch period. Measures of FEV₁ were conducted before exposure and after approximately 1, 2, 3, 4.6, 5.6, and 6.6 hrs, while respiratory symptoms were recorded after each exercise period. The post-exposure percentage

change in FEV₁ and respiratory symptoms for both square wave and triangular exposures to 0.08 ppm were significantly greater than control, 0.04 ppm, and 0.06 ppm exposure, but did not differ from each other. The percentage change in FEV₁ and total symptom severity were significantly different from pre-exposure at 4.6 h following triangular exposure (when the ozone concentration was 0.15 ppm), and at 6.6 h for square wave exposure (ozone concentration was 0.08 ppm). Exercise following 6.6 h of 0.08 ppm ozone exposures (both square wave and triangular exposure) induced a statistically significant rapid shallow breathing pattern, which did not reach statistical significance following 0.04 and 0.06 ppm exposures. The authors also noted a decrease in FEV₁ and an increase in reported respiratory symptoms following both square wave and triangular exposure to 0.06 ppm ozone, though using basic statistical analysis, these were not statistically significant. Indeed, apparent monotonic concentration-related reductions in percentage change in FVC and FEV₁ and increases in respiratory symptoms (pain on deep inspiration, and total subjective symptoms) post-exposure occurred across all exposure levels. In addition, as has been observed in other studies, there was considerable variation in individual responses to ozone exposure, with 3% of the subjects exposed to 0.06 ppm and 17% of the subjects exposed to 0.08 ppm exhibiting >10% FEV₁ decrements, compared with respective group mean decrements of <2% and 5% (US EPA 2006 Ozone AQCD, pp. 8–18), with individual adverse responses even at the 0.04 ppm level.

Another study by Adams (2006b) corroborated earlier findings of stronger associations with triangular exposure profiles compared with square wave profiles. This study was designed to replicate an earlier study (Hazucha et al., 1992) to assess pulmonary responses at 30-min intervals of exercise and rest in 30 male and female subjects exposed to chamber 0.12-ppm square wave or triangular profiles of ozone for 8 h or to filtered air. Post-exposure percentage reductions in lung function were significantly greater in both protocols compared with filtered air exposure, but did not differ significantly from each other. Compared with filtered air exposures, significant declines in FEV₁ were evident sooner in the square wave than the triangular wave exposure (3 vs. 4 h, respectively). The percentage change in FEV₁ for the square wave exposure declined in a near-linear fashion from 1 h through the remainder of the exposure (approximately 2% to -5.74%), while for the triangular exposure, FEV₁ was lowest at 5.5 h (-7.88%) and then gradually increased to -4.34% at 8 h. The percentage change in FEV₁ from pre-exposure was significantly greater for the triangular exposure than for the square wave exposure from 5 h through 7 h, but was non-significantly less than that observed for square wave exposure at 8 h. Despite the lower values in the last hour of exposure, the mean decrement in FEV₁ for the last 4 h of the triangular exposure was more pronounced than square wave exposure (not compared statistically). The pattern of changes in symptoms (pain on deep inspiration and total symptom score) was similar to that for FEV₁.

Ratto et al. (2006) examined single and repeated multi-day exposures to 0.2 ppm ozone in healthy subjects (4 h/d × 1–4 d; n = 15) with intermittent exercise. Similarly to previous findings, it was observed that the greatest changes in symptoms and lung function occurred on the second day and were attenuated by the fourth day. However, pre-exposure FEV₁ was significantly lower on d 3 and 4 compared with d 1, suggesting that full recovery from the effect of the previous day's exposure had not occurred.

Arjomandi et al. (2005a) examined single- and 4-d exposures to 0.2 ppm ozone for 4 h with intermittent exercise in mild asthmatics (n = 14) and observed decreased FVC and FEV₁ on all exposure days, with the largest decrease observed after the second day of a multi-day exposure. After d 2, the decreases in FVC and FEV₁ attenuated and by d 4 the decreases were small, though still statistically significant. FEF_{25–75} and FEF₇₅ showed a similar pattern of change. A very similar pattern was observed for worsening of lower respiratory symptoms, except that by d 4 of the multi-day exposure, there was no significant difference between post-

exposure and pre-exposure symptoms. The authors postulated that the close correlation between the severity of lower respiratory tract symptoms and spirometry suggested that the increase in acute asthma exacerbations after ozone exposure observed in epidemiological studies may have been related to declines in spirometric values or lower baseline lung function and not to the underlying eosinophilic airway inflammatory process.

15.4.3 Effects on Biological Markers

During the review period several more recent studies were published investigating the effects of ozone on various biological markers in an attempt to elucidate the mechanism(s) of toxicity. These studies are summarized in this section, and often involve inflammatory-related markers of the respiratory and/or cardiovascular systems.

15.4.3.1 Acute Exposure

The literature reviewed included studies of healthy and asthmatic subjects exposed to ozone for periods of between 1 and 3 h. The influence of antioxidant supplementation or steroid pre-treatment on the effects of ozone was investigated. In addition, the effects of ozone on inflammatory markers alone or with dust, and its potential to enhance response to allergen challenge, were studied.

Only healthy subjects have been included in studies of the effects of antioxidant supplementation or steroids on ozone-related health effects, as well as the effects of ozone on biological antioxidant capacity. Steck-Scott et al. (2004) examined the effect of ozone exposure and vegetable juice supplementation on plasma and lung macrophage concentrations of carotenoids in a randomized trial of healthy, predominantly male, subjects ($n = 23$). Subjects were randomly assigned to receive either antioxidant supplementation (one 2 oz. can of vegetable juice daily with 250 mg vitamin C + 50 IU vitamin E) or placebo (1 can orange soda daily with placebo pills) for 2 weeks preceding exposure to 0.4 ppm ozone or filtered air for 2 h with exercise. Both groups were maintained on a low carotenoid diet otherwise (<3 mg/d on average). Antioxidant supplementation resulted in increased plasma concentrations of several carotenoids and increased α -carotene concentrations in lung macrophages. Ozone exposure decreased several plasma carotenoids, but only in non-supplemented subjects. This suggests that ozone-induced oxidative stress can be counteracted with antioxidant supplementation.

Mudway et al. (2006) tested the hypothesis that antioxidant supplementation can protect against an environmentally relevant ozone challenge (0.2 ppm ozone for 2 h with moderate exercise) in ozone-sensitive, healthy subjects (study details presented in Section 15.4.2.1). The results indicated that vitamin C and E supplementation did not protect against ozone-induced alterations in any of the measured biological markers in the well-nourished subjects, including markers of inflammation, injury or altered permeability (differential cell counts, IL-6, IL-8, MPO, LDH, total protein, or albumin) in BAL or bronchial wash (BW). This was despite substantially elevated plasma concentrations of these antioxidants and an unexpected finding of increased concentrations of both vitamin C (predominantly as dihydroascorbic acid and vitamin E (α -tocopherol) in the airway and alveolar ELF in BAL and BW after ozone exposure, possibly indicating mobilization of ascorbate to the surface of the lung.

Morrison et al. (2006) exposed groups of five to seven healthy subjects for 1 h via face mask with intermittent exercise to 0.1 or 0.4 ppm ozone. A significant increase in neutrophils measured both as a percentage (compared with 6 h after exposure to 0.1 ppm or 1 h after filtered air exposure) and absolute number (compared with 6 h after exposure to 0.1 ppm ozone) was observed in BAL 6 h after exposure to 0.4 ppm ozone. Exposure to 0.4 ppm ozone

was associated with the volume of ELF, which followed a pattern of increasing 1 h after exposure but declining to levels still greater than pre-exposure after 6 h. While this may be an indicator of increased epithelial permeability, increases in albumin, another marker of epithelial permeability, were not observed in BALF or plasma samples. The authors reported that no biologically relevant changes (increases would indicate increased oxidative stress) in antioxidant capacity or glutathione concentrations in BAL were observed. The only significant increase was in neutrophil percentage and numbers in BAL observed 1 h after exposure to 0.4 ppm ozone compared with pre-exposure, whereas declines in superoxide anion production by BAL leukocytes and products of lipid peroxidation were observed.

The influence of steroid pre-treatment on inflammatory markers after ozone exposure was studied using exhaled breath condensate and induced sputum. Montuschi et al. (2002) exposed nine healthy male and female adults to 0.4 ppm ozone for 3 h with exercise after 2 weeks of twice-daily inhalation of 800 mg budesonide or placebo. In both groups, ozone exposure caused an increase in 8-isoprostane, an indicator of oxidative stress levels, in exhaled breath condensate 4 h post-exposure. Increased absolute neutrophil cell counts and percentage macrophage cell counts were observed in induced sputum 4 h post-exposure. Neither response was affected by pre-treatment with inhaled steroids.

In the only new study that compared the effects of ozone in healthy and asthmatic subjects, no differences in the ozone-modulated expression of surface markers on inflammatory cells were reported. Alexis et al. (2004) employed sputum induction and peripheral blood analysis to examine whether circulating levels of the human surface antigen CD11b in peripheral blood phagocytes and mCD14 in airway macrophages play a role in the inflammatory response following chamber exposure to 0 or 0.4 ppm ozone for 2 h in healthy subjects ($n = 15$) or mild asthmatics ($n = 9$) exercising intermittently. The results indicated that baseline expression of CD11b on circulating monocytes and neutrophils and mCD14 expression on airway macrophages was increased in relation to the magnitude of neutrophil response 4–6 h following exposure to 0.4 ppm ozone; this occurred to a similar degree in both asthmatic and healthy subjects. The association between CD11b and airway neutrophilia was previously observed after endotoxin-induced inflammation (Alexis et al., 2003), suggesting that CD11b expression may prove to be a useful general marker for individual susceptibility to non-specific airway inflammation from air pollutants. Adequate sputum samples were not obtained consistently pre- and post-exposure for all subjects, reducing the number of paired observations.

Arjomandi et al. (2005b) examined whether changes in sputum induction and BAL indices of airway inflammation were predictive of each other by exposing nine asthmatic subjects to ozone (0.4 ppm) or filtered air for 2 h with intermittent exercise; there was a minimum of 3 weeks between exposures. Eighteen hours post-exposure, changes in PMN percentages in sputum samples were poorly correlated with the changes seen in BAL fluid samples. Compared with filtered air, ozone-induced increases in PMN percentages in BFX (bronchial fraction of BAL fluid) and BAL fluid were of greater statistical significance than those in induced sputum ($p = 0.001$, $p = 0.008$ and $p = 0.045$, respectively) potentially as a result of less variation in PMN percentages in BFX and BALF. The authors noted several factors that may have affected the degree of variation between samples (e.g. different composition of respiratory tract lining fluid (RTLFL) between sputum, BAL and BFX sampling; greater inter-subject differences in producing sputum samples compared with BAL or BFX; and more difficulty in processing and scoring sputum slides).

Molhave et al. (2005) investigated interactions between ozone and resuspended office dust in atopic individuals (four males and four females). Subjects were exposed for 3 h by inhalation in a chamber to ozone alone, dust alone, or combined exposure to ozone and dust (0.3 ppm and $75 \mu\text{g}/\text{m}^3$ respectively). Exposures were conducted in random order on the same day of the

week, separated by 1 week. Compared with ozone alone or dust alone, combined exposure was associated with a significant increase in the number of eosinophils in nasal lavage fluid ($p = 0.044$). In addition, a non-significant increase in neutrophils and non-significant decline in IL-8 levels were observed after the combined exposure compared with either individual exposure. No significant effects were associated with exposures to ozone or dust alone and no changes in cytokine levels were observed. The small number of subjects and the omission of a clean air exposure reduce confidence that the observed changes are due to the combined exposure.

Chen et al. (2004) investigated whether exposure to ozone enhances the early bronchoconstrictor response and the late airway inflammatory response to inhaled HDMA in sensitized asthmatic subjects. Thirteen males and one female subject were randomly exposed to 0.2 ppm ozone or filtered air for 1 h while exercising followed by an allergen challenge (*Dermatophagoides farinae*). Exposures were separated by at least 4 weeks. Similarly to earlier studies that employed low-dose ozone exposure protocols (Ball et al., 1996; Hanania et al., 1998) the results did not demonstrate a significant effect of ozone exposure on bronchoconstrictor response to HDMA. The results of this study did suggest a trend toward greater neutrophilia in the proximal airways 6 h after ozone-HDMA exposure compared with air-HDMA exposure. No differences in the levels of various markers of inflammation (MPO, tryptase, ECP, fibronectin, IL-5, IL-6, IL-8, GM-CSF, TGF-beta1, and TGF-beta2) were observed. Considering the relatively low effective dose of ozone used in this study, the authors suggested that a modest effect on the late-phase inflammatory response from ozone may have gone undetected in the background of a larger inflammatory response to HDMA.

15.4.3.2 Prolonged and Repeated Exposures

Recent controlled human exposure studies of the effects of prolonged and repeated exposure to ozone on biomarkers are limited to three studies of subjects exposed for 4-h periods.

Polosa et al. (2004) tested the hypothesis that nasal epithelial cells respond to ozone-induced oxidant stress by modulating expression of EGFR and its ligands, EGF and TGF- α . To dissect out cellular mechanisms leading to an increase in EGFR after ozone exposure, neutrophil release and EGFR expression were examined in nasal epithelial cell cultures exposed *in vitro* to ozone or TNF- α . In the clinical part of the study, 10 healthy subjects were randomly exposed at rest to 0 or 0.4 ppm ozone for 4 h, with exposures separated by at least 2 weeks. In nasal biopsy specimens taken 6 h after exposure, a marked and consistent increase in the level of expression of EGFR and its ligands, EGF and TGF- α , was observed with ozone exposure compared with air-only exposure. A significant increase in the total number of neutrophils in nasal epithelium and submucosa was also observed, in agreement with previous studies using BAL. Activated neutrophils are a significant source of proinflammatory cytokines, including TNF- α . A significant positive association was observed between the number of neutrophils in the epithelium and the level of EGFR expression in the nasal epithelium after ozone exposure. A lack of direct effects of ozone on EGFR *in vitro* led the authors to suggest that upregulation of EGFR is indirect and results from the pro-inflammatory effects of ozone (*in vitro* stimulation with TNF- α resulted in a time- and dose-dependent increase in EGFR expression).

Arjomandi et al. (2005a) tested the hypothesis that repeated daily exposures to ozone for 4 d (0.2 ppm; 4 h/d with intermittent exercise) cause a progression of airway inflammation compared with single-day exposures in 14 subjects with asthma. Exposure series were separated by at least 3 weeks. Bronchoscopy was performed 18 h after either 1-d exposure or the last day of 4-d exposure. Increased total leukocytes in Bfx (25%) and BAL fluid (49%) were observed after 4-d exposure compared with 1-d exposure, primarily due to an increase in AMs in the lavage fluid (an increase of 57% in Bfx and 64% in BAL). Contrary to the study hypothesis, repeated exposures did not result in an enhancement of the acute neutrophilic

response in subjects with asthma compared with a single short-term exposure. In fact, there was some attenuation of lavage neutrophilia after multi-day exposure, though it did not reach statistical significance. The sample size was limited, however, and no filtered-air control exposure was assessed. The significant increase in macrophages was suggested to indicate a possible role for these cells in the chronic response to oxidant-induced injury. Macrophages can either produce or prevent further oxidative injury and have been implicated in airway remodelling processes.

Ratto et al. (2006) examined single- and multi-day exposure to 0.2 ppm ozone in healthy subjects (4 h/d; n = 15) with intermittent exercise. Increased neutrophils and decreased macrophages were observed in induced sputum 18 h after 4 d of exposure vs. a single-day exposure. The lack of attenuation of neutrophilic inflammation in induced sputum after repeated exposure compared with a single exposure is in contrast to the findings of previous studies in which attenuation of this response was observed in BALF (e.g. Christian et al., 1998) and could be due in part to a differential response between proximal and distal airway compartments. Sputum induction is believed to preferentially sample proximal airways compared with BAL, which preferentially samples distal airways and alveoli. This adds to the body of evidence suggesting that differential airway compartmental responses to ozone occur in humans.

15.4.4 Cytotoxicity, Genotoxicity and Other Effects

No controlled human exposure studies on the cytotoxicity or genotoxicity of ozone were reported in the 1999 Ozone SAD. As discussed in Section 15.4.1, the primary focus of studies in this area reviewed in the US EPA 2006 Ozone AQCD was the modulating effects of different genetic polymorphisms of antioxidant enzymes and inflammatory genes on sensitivity to ozone. Only one genetic study published in the review period was identified.

Cytogenetic damage in buccal (cheek) epithelia and peripheral lymphocytes were studied in 15 healthy young adults exposed to ozone (0.2 ppm for 4 h with intermittent exercise) (Chen et al., 2006). Both a longitudinal observational study and a controlled ozone exposure study were conducted; only the latter is summarized here. Subjects in the upper and lower 10th percentile of FEF₂₅₋₇₅ from the larger longitudinal cohort were selected for the controlled exposure study. Increased micronuclei frequency in degenerated buccal cells was observed 9–10 d post-exposure, as was an increase in pycnotic cells (a reflection of cell necrosis). A borderline significant increase in micronuclei and a 73% increase in nucleoplasmic bridge frequency were observed in binucleated lymphocytes 18 h post-exposure. The correlation between micronuclei in buccal cells and micronuclei in binucleated lymphocytes was significant post-exposure but not pre-exposure. The authors concluded that the results substantiate the hypothesis that ozone can induce cytogenetic damage in healthy adults, likely due to systemic oxidative stress, as a similar response was seen in blood lymphocytes and buccal cells. The study has several weaknesses, however: no filtered air control group was examined, the age and sex of subjects were not provided, and it was unclear why buccal cells were not sampled until 9–10 d post-exposure (vs. 18 h post-exposure for peripheral blood lymphocytes). A single dose of ozone was examined, precluding dose–response evaluation; and finally, it was unclear why subjects in the upper and lower 10th percentile of FEF₂₅₋₇₅ were selected for the controlled exposure study (from the larger cohort followed in the longitudinal study).

Brook et al. (2002) reported the results of a study in which healthy adults exposed for 2 h to Toronto CAP (ca. 150 µg/m³ as PM_{2.5}) with added ozone (ca. 120 ppb) had significant brachial artery vasoconstriction compared with filtered air inhalation. There were no significant effects on endothelial-dependent and -independent vasomotion determined by flow-mediated dilatation and nitroglycerin-mediated dilatation, respectively. No ozone-only exposure was included in this

study. In subsequent reports, the brachial artery vasoconstriction was significantly correlated with the OC and EC content of the ambient PM, but not with total PM or a number of trace elements and inorganic constituents (Urch et al., 2004). There was also a significant decrease in diastolic blood pressure (but not systolic blood pressure or heart rate) with CAP+ozone exposure compared with filtered air, which was significantly correlated with OC concentration but not total PM_{2.5} mass (Urch et al. 2005).

15.4.5 Summary and Considerations: Controlled Human Exposure Studies

In controlled studies of humans reviewed in this report and in previous assessments, exposure to near-ambient levels of ozone caused a variety of effects, almost exclusively in the respiratory system. Effects reported include decreased inspiratory capacity, mild bronchoconstriction, shallow rapid breathing during exercise, decreased measures of lung function including FVC and FEV₁, as well as increases in respiratory symptoms, AHR, inflammation, immune system activation, and epithelial injury. There is a large degree in variability in physiologic and symptom responses to ozone among healthy adult subjects, but responses tend to be reproducible within a given individual over a period of several months. In general, findings from the limited number of newer studies confirmed many of the above effects described in previous Canadian and American assessments.

The results of new studies support previous findings of the attenuation (i.e. observation of reduced response) of ozone's effects on pulmonary function and symptoms following repeated exposure to ozone with less attenuation of inflammatory markers. Therefore, this attenuation of pulmonary function and respiratory symptoms is not necessarily an indication of attenuation in overall toxicity. As found in previous studies, the strongest effects were observed on the second day of exposure with marked attenuation by the fourth day, though complete recovery was generally not observed, and the US EPA 2006 Ozone AQCD noted that hyperresponsive individuals took longer to return to baseline values. In contrast to previous studies of healthy subjects no attenuation of the neutrophil response was observed in a recent study. This difference may have been related to sampling techniques: earlier studies employed BALF sampling of the distal airways, and more recent studies used sputum samples (proximal airways). This hypothesis is supported by the findings of another recent study in which sputum and BAL levels of PMN percentages were poorly correlated. In one of the first studies to address attenuation in asthmatics, non-significant attenuation of neutrophilic inflammation in BALF samples was reported following repeated exposure to ozone.

New studies characterized ozone-induced changes in a novel marker, A_p: a CO₂ expirogram parameter that measures the gas transport process as the peripheral cross-sectional area from the alveolar plateau. Its association with ozone uptake in the distal lungs but not with FEV₁ or V_d (markers of changes in the conducting airways) suggested that it was a marker of pulmonary response in the distal airways. CD11b was also identified as a potential marker of individual susceptibility to air-pollution-related non-specific airway inflammation in asthmatics and healthy subjects.

With respect to factors that modify individual responses to ozone, during exercise spirometric and symptom responses are observed at lower concentrations, and hence most studies expose subjects while engaged in physical activity. The US EPA 2006 Ozone AQCD also identified age, the profile of exposure (e.g. triangular vs. square wave) and antioxidant supplementation as modifying factors. In the recent literature, the results of one study confirmed the EPA's conclusion that stronger declines in lung function and symptoms are observed during triangular

wave, as compared with square wave, exposure. The triangular exposure protocol simulates ambient ozone levels that vary diurnally, peaking mid-afternoon with lower concentrations in the morning and evening. In contrast, the new literature presents conflicting evidence of a protective effect of antioxidants. While earlier studies found that dietary exposure to antioxidants reduced the effects of ozone on spirometry and bronchial hyperresponsiveness (but not symptoms or inflammation), only one recent study supported the concept that ozone-induced oxidative stress can be counteracted with antioxidant supplementation. The results of another study suggested no protection against inflammation, injury or altered permeability in BAL or BW (even while reporting novel findings of movement of vitamin C into human RTLF, which the authors suggested may confer protection against subsequent oxidative challenges). No new controlled human studies of the genetic differences in susceptibility were reviewed to confirm the findings reviewed in the US EPA 2006 Ozone AQCD, in which ozone-related changes in lung function, markers of inflammation and oxidative stress were dependent on subject genotype. In these studies, the subjects' susceptibility to ozone-related effects on pulmonary function and airway inflammation was increased or decreased in relation to genetic polymorphisms in specific antioxidant and inflammatory genes.

Asthmatics continue to be the only subgroup with pre-existing disease for which there are sufficient data to draw conclusions regarding sensitivity compared with healthy subjects (though for ethical reasons little or no data exist on the effects of ozone in moderate to severe asthmatics). In earlier assessments, asthmatic subjects had greater alterations in spirometric and inflammatory parameters, and in bronchial reactivity, than their healthy counterparts. Since asthmatic patients have lower baseline values for most spirometric parameters than healthy subjects, a further decrease in FEV₁ caused by ozone could potentially take it below the threshold associated with asthma attacks. In the recent literature, the effects of ozone in asthmatics include increases in immune cells in BAL after multi-day exposures compared with a single acute exposure and attenuation of pulmonary function but not neutrophil levels following repeated exposures. These effects are similar to those reported in earlier studies of healthy subjects. There was some evidence from one study to suggest that ozone sensitivity based on FEV₁ was associated with allergen sensitivity.

As a result of the various factors that modify the individual responses to ozone listed above, a wide range of effect levels have been reported in the available controlled human exposure studies. Significant effects on lung function and respiratory symptoms were observed at concentrations as low as 0.12 ppm after 1–4 h exposure and at concentrations as low as 0.08 ppm after 6–8 h exposure in studies reviewed in the 1999 Ozone SAD and in the US EPA 2006 Ozone AQCD. However, in the study in which exposure–response was best characterized (Adams, 2006a) the author also noted a decrease in FEV₁ and an increase in reported respiratory symptoms following both square wave and triangular exposure to 0.06 ppm ozone though using basic statistical analysis, these were not statistically significant. Indeed, apparent monotonic concentration-related reductions in percentage change in FVC and FEV₁ and increases in two measures of respiratory symptoms post-exposure occurred across all exposure levels (0.04 to 0.08 ppm). In addition, as has been observed in other studies, there was considerable variation in individual responses to ozone exposure, with 3% of the subjects exposed to 0.06 ppm and 17% of the subjects exposed to 0.08 ppm exhibiting >10% FEV₁ decrements, compared with respective group mean decrements of <2% and 5% (US EPA 2006 Ozone AQCD, pp. 8–18), and with adverse responses in some individuals even at the 0.04 ppm level. Considering the evidence of pulmonary effects at the two lowest concentrations tested, the very limited statistical power in all of the studies, and the body of evidence indicating that some individuals are markedly more sensitive to the effects of ozone on the respiratory system, it is not possible to identify a concentration that is without effect based on the available controlled human exposure studies.

To date there has been little research in controlled studies in humans into the effects of ozone in combination with other pollutants. At the time of the 1999 Ozone SAD a synergistic association with SO₂ in inducing bronchial hyperreactivity was observed, while NO₂ was shown to increase pulmonary function responses after exposure to ozone. The US EPA 2006 Ozone AQCD concluded that clinical studies provide only weak evidence to support the hypothesis that exposures to mixtures of pollutants have greater effects than single-pollutant exposures. A lack of new evidence in this area is driven by studies of co-exposures that failed to include ozone-only exposures for comparison purposes.

15.5 Acute Exposure Epidemiology

Epidemiological studies represent a critical way to examine the possible effect of air pollution on population or community health responses. Epidemiological studies of the potential effects of ambient ozone on human health explore the associations between changes in ambient levels of ozone and the occurrence of particular health endpoints. Since these observed relationships are often of small magnitude and are vulnerable to confounding from factors such as seasonal cyclic variations and co-pollutants, a rigorous statistical analysis is necessary in order to detect any existing effect.

Six major epidemiological study designs can be identified that focus on either the acute or the chronic effects of airborne pollution:

Time-series studies, which investigate the acute effects of ozone—i.e. temporal associations between the daily variation in ozone levels and daily counts of mortality, hospital admissions and emergency room visits;

Case-control studies, which compare the risks of elevated exposures to ozone in people with a certain disease (cases) to those without the disease (controls);

Case-crossover studies, a variant of case-control studies, which compare individual health outcomes and the air pollution level at the time of the event to conditions that prevailed before and after the health problem occurrence. This type of study was conceived to evaluate the effect of transient exposure on acute events;

Panel studies, which investigate the association between variation in air pollutant levels and repeated measurements of health outcomes in a defined group of subjects;

Cohort studies, which explore chronic effects—i.e. the association between cumulative exposure and mortality or morbidity endpoints such as chronic diseases and lung function decrements;

Cross-sectional studies, which focus on the association between current exposure and endpoints such as mortality and cardiovascular or respiratory effects. Such studies have often been applied to the examination of long-term or chronic effects in relation to air pollution, but this design can also be used to study acute effects of air pollution.

Most of the recent acute effects epidemiological studies have been time-series in nature. However, the same time-series data can be analyzed as time-series (e.g. Poisson regression) or with case-crossover methods, and more investigators have used this latest approach in the past few years. Recent studies of acute mortality and hospitalizations include investigations of both respiratory and cardiovascular endpoints.

For time-series studies, both the series of daily health outcome rates and the series of daily air pollution concentrations are subject to strong seasonal, sub-seasonal, and day-of-the-week variations as well as long-term trends. At one time, GAMs with LOESS smoothers had become the standard method to adjust for these temporal fluctuations in time-series studies. However, this technique was found to yield biased estimates of risks and standard errors if the default settings in the GAM function of the S-plus software package were used, although systematic reanalyses using more appropriate techniques indicated that the association with air pollution persisted in the majority of studies (HEI, 2003; this work focused on studies with PM, but the findings are applicable to analyses for other pollutants that use this methodology). Most researchers have subsequently employed techniques that did not suffer from this bias (e.g.

GLM with natural splines, or GAMs with stricter convergence criteria). In this review, when GAM methodology that may suffer from this bias was used, this is noted in the study account.

15.5.1 Mortality

15.5.1.1 Summary of Previous Assessments

At the time of the 1999 Ozone SAD, evidence from the majority of time-series studies conducted in North America, South America and Europe indicated a positive and consistent relationship between acute exposure to ambient ozone and daily non-accidental mortality that was independent of other co-pollutants. These associations were observed across widely varying climatic conditions and pollutant mixtures in the study locations, and could not be explained on the basis of yearly trends, day-to-day variations, epidemics or weather. In several studies these effects occurred at mean ozone levels between 20 and 75 ppb, below the existing Canadian air quality objectives. In addition, the ozone concentration–response relationship was approximately linear in most studies (in one case down to less than 10 ppb), and these studies did not show evidence of thresholds at low concentrations. Furthermore, several studies reported that ozone was associated with cardiovascular mortality but not respiratory mortality, possibly because of limited statistical power as a result of the proportionally fewer deaths in the latter category.

The US EPA 2006 Ozone AQCD concluded that short-term exposure to ozone was clearly associated with daily mortality. In particular, findings from a multi-city US study provided strong evidence of an important relationship between ambient ozone and acute all-cause (non-accidental) mortality (Bell et al., 2004) and these findings were supported by subsequent meta-analyses (Bell et al., 2005; Ito et al., 2005b; Levy et al., 2005). Some studies noted heterogeneity of risk estimates across cities and studies, which was partly attributed to likely differences between populations (pollution characteristics, use of air conditioning, time-activity patterns, socioeconomic factors, etc.) as well as model specifications. Single-city studies reported similar ozone–mortality associations, and in general ozone effects were robust to adjustment for PM and other pollutants, as well as to adjustment for potential confounders such as time and weather. In addition, while most studies reported associations over short-term single-day lag periods, the results of several studies indicated that longer exposure averaging times may also be relevant to mortality, suggesting that the effects of acute ozone exposure on mortality may persist over several days. Many studies relied on annual data, and this may have led to an underestimation of risk estimates, as ozone is primarily a warm-season pollutant. Indeed, stratification by season in some studies indicated that effects were strongest in the warm season. Some studies investigated specific subcategories of mortality: though most of these studies had limited statistical power to detect associations and lacked information on contributing causes of death, a meta-analysis reported a slightly greater risk of cardiovascular mortality than total mortality. The few studies of subpopulations with underlying cardiopulmonary diseases also had limited statistical power, but there was suggestive evidence that severe asthmatics and the elderly may be more susceptible to ozone-related mortality. Finally, while the US EPA did not find any evidence of a threshold in most studies of the relationship between ozone and mortality, they did note that even if a threshold were to exist it would likely be near the lower limit of US ambient concentrations.

15.5.1.2 Mortality Studies

Acute mortality studies are the most numerous among recent studies of the health effects of ozone. Most commonly, investigators have examined the relationship between increases in ambient ozone concentrations and cardiovascular, respiratory, or total non-accidental mortality.

In previous assessments summarized in Section 15.5.1.1, ozone was consistently associated with total non-accidental mortality and in some cases cardiovascular mortality. The results of more recent studies generally support these associations.

In presenting the results of the epidemiology studies of ambient ozone reviewed in this assessment, in this section and subsequent ones the highest risk estimates (significant or non-significant) reported in each individual study from Canada, the US, Europe and Australia are generally presented. Results for studies from other locations, which are potentially less relevant to Canada because of differences in such things as exposure levels, climate and lifestyle, are generally discussed in less detail. Wherever relevant and possible, to allow comparisons across studies, risk estimates (risk/rate ratios as well as relative risks and 95% confidence intervals) were converted to a percentage risk increase per a standardized increment of ozone, assuming a linear association between the particulate air pollutant and specific health outcomes.

A variety of daily ozone exposure metrics are used in the existing health studies, most often the 1-h maximum average within a 24-h period (1-h max), the maximum 8-h average within a 24-h period (8-h max), and the 24-h average. To facilitate comparisons between studies, the percentage risk increase estimates for these various durations need to be presented by a uniform exposure increment. In presenting the results of individual studies, percentage risk increases for 8-h max ozone were estimated for a standard increment of 10 ppb. Risk estimates for 1-h max and 24-h average ozone were calculated for increments of 13.3 ppb and 6.7 ppb, based on the ratios of the standardized increments used in the US EPA 2006 Ozone AQCD (40 ppb for 1-h max, 30 ppb for 8-h max, and 20 ppb for 24-h average). In this manner, the percentage risk increase estimates are comparable across the different metrics.

Rainham et al. (2005) examined the influence of weather on pollutant-related mortality in Toronto, ON. Six typical air masses (plus transitional categories) were identified using temperature, dew point, east–west winds, north–south winds, cloud cover and sea level pressure for a 19-year period (1981–1999). Using GLMs adjusted for temporal trends, serial autocorrelation and day of week, it was observed that an unspecified change in ozone (mean 24-h annual average 17.3 ± 7.3 ppb) was associated with cardiorespiratory mortality in the summer at lag 2 d (RR = 1.002 (95% CI: 1.001–1.003); mean 24-h average 25.2 ± 10.2 ppb) but not in the winter. Under specific air masses, which were characteristically similar, stronger associations with ozone were observed: RR = 1.003 (95% CI 1.001–1.006) for dry-moderate air masses and RR = 1.014 (95% CI 1.003–1.025) for dry-tropical. Other significant associations were observed between ozone and non-cardiorespiratory mortality for dry-moderate air masses and total mortality for dry-tropical air masses. There was no clear explanation for the difference in effects between air masses; however, the authors concluded that the association between air pollutants and mortality was influenced by subtle changes in meteorological conditions. Associations between mortality and PM_{2.5}, NO₂, CO and SO₂ were also observed. No multi-pollutant models were investigated.

Bell et al. (2006) examined the relationship between low-level ambient ozone exposures and mortality in 98 American cities. Data for all-cause non-accidental mortality were obtained from the NMMAPS and four analytical approaches were employed: a linear approach (traditional), a subset approach restricted to 1-d lag ozone concentrations below set concentration cut-offs, a threshold approach (tested from 0 to 60 ppb), and a spline approach that allowed relative rates (RRs) to vary across ranges of ozone levels. In the linear model, a 6.7 ppb increase in lag 0–1 d average ozone levels was associated with a 0.21% (95% PI 0.11–0.31%) increase in mortality, with lesser risk estimates reported over shorter lag periods (0.17% (95% PI 0.08–0.25%), 0.12% (95% PI 0.05–0.20%), and 0.09% (95% PI 0.02–0.17%) for lags 0, 1 and 2 d respectively per 10 ppb). When only days with ozone concentrations below the CWS (65-ppb 8-h daily max) were included, the increase in mortality for a 6.7-ppb increase in lag 0–1 day ozone was 0.19% (95%

PI 0.07–0.30%). Using data below set concentration cut-offs, risk estimates for successively lower cut-offs were similar to the ones obtained using all data, and were reduced only when the lag 0–1 d average ozone was ≤ 10 ppb (roughly equivalent to 15–19 ppb for the maximum 8-h average). The threshold model was only a nominally better fit for the data than the linear model, and the exposure–response curve generated using the spline model approximated linearity at concentrations greater than 10 ppb lag 0–1 d average ozone (only graphical data presented). Therefore, only at concentrations of approximately 0–10 ppb was there little evidence of an association between ozone and mortality, though it is considered likely that in this range there were too few observations to determine if a threshold exists. The authors concluded that if a threshold does exist, it is likely below current American guidelines and likely close to background concentrations

Simpson et al. (2005a) examined the association between ambient ozone concentrations (range of mean 1-h max 24.35–33.78 ppb) and daily mortality in four Australian cities (Perth, Melbourne, Sydney and Adelaide) between 1996 and 1999. Single-city estimates were not presented, but in pooled analyses a 10-ppb increase in 4-h max ozone concentrations was associated with an increased risk of respiratory mortality at lags 0 d (2.32% (95% CI 0.50–4.28%) and 0–1 d (2.53% (95% CI 0.30–4.90%)). In comparison, a 13.3-ppb increase in 1-h max ozone levels was associated with 2.69% (95% CI 0.4–4.87%) and 2.95% (95% CI 0.27–5.69%) increases in the risk of respiratory mortality for lag 0 d and lag 0–1 d, respectively. Ozone was not associated with total mortality (0.53% (95% CI -0.13–1.07%) at lag 0 d) or cardiovascular mortality (0.80% (95% CI -0.13–1.74%) at lag 0 d), though risk estimates were non-significantly increased for most lags for both of these categories; however, NO₂ and bsp were each associated with total, respiratory and cardiovascular mortality.

Biggeri et al. (2005) used classical meta-analysis techniques to investigate the associations between air pollutants and total, cardiovascular, and respiratory mortality in eight Italian cities from 1990 to 1999. Ozone analyses were limited to data from May to September with daily 8-h max ozone concentrations ranging from 54.5 to 58.8 ppb. In contrast to the Australian multi-city analysis (Simpson et al., 2005a), in the Italian meta-analysis a 10-ppb increase in warm-season ozone was associated with increased total mortality (1.64% (95% CI 0.34–2.98%)) and cardiovascular mortality (2.86% (95% CI 0.72–5.00%)) but not respiratory mortality (-0.56% (95% CI -5.90–4.94%)).

Parodi et al. (2005) employed a time-series approach to examine the association between ozone and daily mortality in Genoa, Italy, between 1993 and 1996. Daily mean ozone concentrations were 32.15 ± 16.55 ppb for the whole study period and 40.95 ± 14.8 ppb for the warm seasons. The investigators considered 24-h mean, 8-h mean (10 a.m. to 6 p.m.), and 1-h max ozone levels at lags of 0–2 d and adjusted for long-term trends, seasonality, holidays, weekends, and weather conditions. A 6.7-ppb increase in 24-h mean ozone was associated with total mortality at a 1-d lag (1.07% (95% CI 0.05–2.09%)) with a slightly stronger effect observed when analyses were limited to the warm season (1.31% (95% CI 0.03–2.65%)). Ozone was also associated with cardiovascular mortality for the entire period and the warm period at lags 0 and 1 d, with the strongest effect for a 1-d lag in 24-h mean ozone concentration during the warm season (2.68%, 95% CI 0.56–4.98%). Risk estimates were not clearly greater for older adults (>75 years of age) than for all ages, except for ozone-related total mortality, particularly at lag periods of 2 d. Findings were generally similar with the 8-h mean and 1-h max ozone concentrations.

Diaz et al. (2004) examined the relationship between ambient air pollution and total daily mortality among children <10 years of age in Madrid, Spain, between 1986 and 1997. Specifically, Poisson regression models were used to examine the association between ozone and mortality adjusted for meteorological variables (temperature and relative humidity) and

other air pollutants (SO₂, NO_x, and TSP). Annual, summer, and winter periods were considered separately. Ambient ozone was not associated with an increased risk of mortality in any of the time periods (data not provided), though there were significant associations with TSP in winter, and with TSP and NO_x in summer; however, mean ozone levels were low throughout the study period (22.8 ± 14.3 µg/m³ (11.4 ± 7.2 ppb))

Forastiere et al. (2005) conducted a case-crossover study to examine the association between air pollution and out-of-hospital IHD deaths in Rome, Italy, between 1998 and 2000. Ambient ozone (mean 8-h average 118 µg/m³ (59 ppb), April–September only) was not significantly associated with out-of-hospital mortality from IHD for any lag time tested; in fact, most risk estimates were non-significantly decreased. However, significant associations were observed for other pollutants (PNC, PM₁₀ and CO).

Fischer et al. (2003) examined the relationship between daily air pollution and total, pneumonia, COPD, and CVD-related mortality in the Netherlands between 1986 and 1994. For specific categories of death, a 10-ppb change in lag 1 d ozone concentration (median 8-h average 47 µg/m³ (20.35 ppb)) was associated with increased risk of COPD mortality for the <45-year-old age group (10.66% (95% CI 3.11–18.76%)), pneumonia mortality for the 65–74 age group (6.44% (95% CI 2.05–11.02%)) and the ≥75 age group (4.26% (95% CI 2.96–5.56%)), and CVD mortality for the ≥75 age group (0.94% (95% CI 0.58–1.30%)). For total mortality, ozone-related risks for the same increment and lag were significantly or marginally increased in adults aged 45–64, 65–74 and ≥75 years (data provided only in a figure).

Hong et al. (2002) examined the association between daily air pollution and hemorrhagic and ischemic stroke mortality in Seoul, South Korea, between 1991 and 1997. The mean 8-h daytime ozone concentration was 22.0 ± 12.4 ppb. The data were analyzed with a GAM using LOESS smoothers; the convergence criteria employed were not discussed. Ozone was not significantly associated with an increased risk of hemorrhagic stroke mortality, but an increased risk of ischemic stroke mortality was associated with lag 3 d ozone levels (3.42% (95% CI 1.15–5.66%)) per 10-ppb increase in mean 8-h ozone). In general, effect estimates for ozone remained significant when other pollutants (TSP, SO₂, NO₂ and CO) were included in two-pollutant models, and evidence of a possible threshold effect was observed for ischemic stroke mortality at 25 ppb. Other pollutants (SO₂, NO₂ and CO) were also associated with increased risk of ischemic stroke mortality.

Finally, Wong et al. (2002) conducted a time-series analysis to examine the influence of air pollution on cardiovascular and respiratory mortality in Hong Kong (1995–1998). Mean 8-h average ozone concentrations were 33.93 ± 23.15 µg/m³ (17.0 ± 11.6 ppb) and lags of 0–5 d were tested. A 10 ppb increase in 8-h mean ozone was associated with an increased risk of mortality from respiratory diseases at lag 2 d (1.97% (95% CI 0.79–3.16%)), from COPD at a 0–4 d cumulative lag (6.78% (95% CI 3.36–10.45%)), and from IHD at lag 3 d (1.77% (95% CI 0–3.56%)), as well as with marginally non-significantly increased risks for pneumonia and influenza mortality. Effect estimates for ozone remained stable in multi-pollutant models.

15.5.1.3 Summary and Considerations: Acute Mortality

In the epidemiological studies of acute exposure to ambient ozone reviewed in this assessment and in earlier assessments, the risk estimates associated with total non-accidental mortality were mostly positive, and most of these were statistically significant after adjustment for potential confounders such as time and weather (Section 15.5.1; Figure 15.5; Figures 7-14 and 7-15 in US EPA 2006 Ozone AQCD). Increased ozone-related mortality has been reported in numerous studies from almost all regions of the world, including North and South America, Europe, Australia and Asia, demonstrating consistency of results despite widely varying climatic conditions, pollutant mixtures, and socioeconomic settings. In these studies associations of

mortality with ozone were often robust to adjustment for PM and other co-pollutants, and often the effects of ozone were restricted to the warm season, indicating that this mortality is specific to ozone. (Of the common air pollutants, ozone alone is predominantly a summertime pollutant.)

Ozone-related mortality has been reported in numerous single-city studies of a variety of study designs, as well as in meta-analysis studies, and increasingly in multi-city studies. The latter studies are particularly important in that they do not suffer from publication bias, and they have the statistical power and variety of urban settings to yield more precise estimates of risk and to provide information on such issues as the heterogeneity of risk estimates and the shape of the exposure–response relationship. Among the multi-city studies, the NMMAPS studies of mortality and morbidity in relation to ozone are especially relevant, because of the large size of the database (almost 100 US cities with many years of follow-up), the specific focus on ozone hypotheses testing, and the investigation of several important issues. As discussed in the US EPA 2006 Ozone AQCD, analyses by Bell et al. (2004) revealed significant heterogeneity in the effect estimates from the individual communities, which was partially attributed to differences in pollutant mixtures, air conditioning, time-activity patterns and socioeconomic factors. Heterogeneity among risk estimates in the larger literature also exists, and is likely related to these factors, as well as such things as differences in model specifications among studies. In this study, the largest risk estimate was obtained with a 0-day lag, with diminishing risk estimates for subsequent days, confirming the short-term nature of the effect of ozone on mortality that is seen in most of the literature. However, the risk estimate for cumulative effect from the same day and six previous days was more than twice as large as the same-day estimate, which along with similar findings reported in some other studies, suggests that the effects of ozone may persist over longer periods and that use of single-day lags may underestimate risks. In a study reviewed in this assessment, Bell et al. (2006) investigated the shape of the exposure–response curve for ozone-related mortality. The results of extensive analyses using several approaches indicated that the mortality was related to ambient ozone in an approximately linear fashion at concentrations greater than 10 ppb 24-h average ozone. The authors concluded that, if a threshold for ozone-related mortality exists, it is likely close to background concentrations, which confirms the predominant lack of evidence for a threshold in the earlier literature.

In addition to all-cause mortality, a more limited number of studies have examined ozone-related mortality from broad underlying causes (e.g. cardiovascular) or from specific causes of death. In the studies reviewed in this and earlier assessments, risk estimates were generally positive and often statistically significant for respiratory mortality (Figure 15.6) as well as for cardiovascular mortality (Figure 15.7, also Figure 7-25 in the US EPA 2006 Ozone AQCD). However, the increased risks for respiratory mortality in Figure 15.6 are not entirely consistent, and the US EPA noted that while the risk estimates for deaths from respiratory causes were larger than cardiovascular or all-cause mortality in several studies, in other studies they were smaller or even negative, in contrast to positive findings for total or cardiovascular categories. The apparent inconsistencies in study findings could reflect differences in model specifications, the lower statistical power associated with the typically smaller daily counts for respiratory mortality versus cardiovascular, or the difficulties in assigning cause of death when both respiratory and cardiovascular factors contribute (to which respiratory mortality, as the less common category, might be more susceptible). In contrast, the risk estimates for cardiovascular mortality in the studies reviewed in this assessment and in the US EPA 2006 Ozone AQCD are more consistent; virtually all of them are positive, and many are statistically significant, though some heterogeneity across studies is evident. In general, risk estimates for cardiovascular deaths as a whole are similar to but slightly greater than for all-cause non-accidental mortality, which is not unexpected since cardiovascular deaths account for the largest fraction of total deaths. There is no clear consistency in the ozone-related mortality from more specific causes

in the few available studies, and questions remain with respect to the role of co-pollutants in the observed associations. Similarly, the evidence that mortality associated with ozone is greater in potentially susceptible subpopulations is limited, though there is some suggestion in the few available studies of effects in people with severe asthma or COPD, and in the elderly.

Figure 15.5 Risk estimates for total mortality per 10-ppb increase in 8-h ozone/6.7 ppb increase in 24-h ozone concentration in single-pollutant models

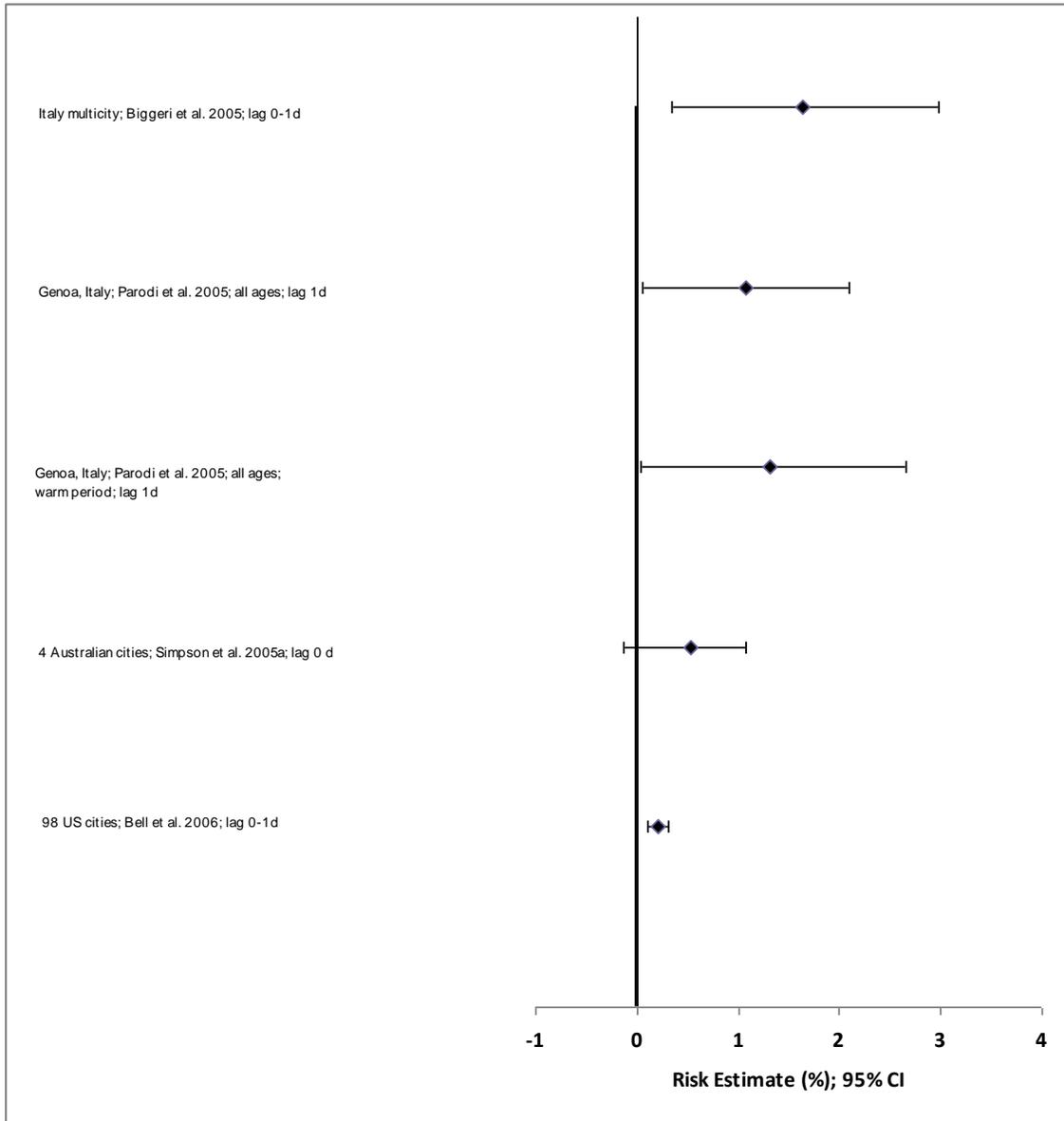


Figure 15.6 Risk estimates for respiratory mortality per 10-ppb increase in 8-h ozone/13.3-ppb increase in 1-h ozone concentration in single-pollutant models

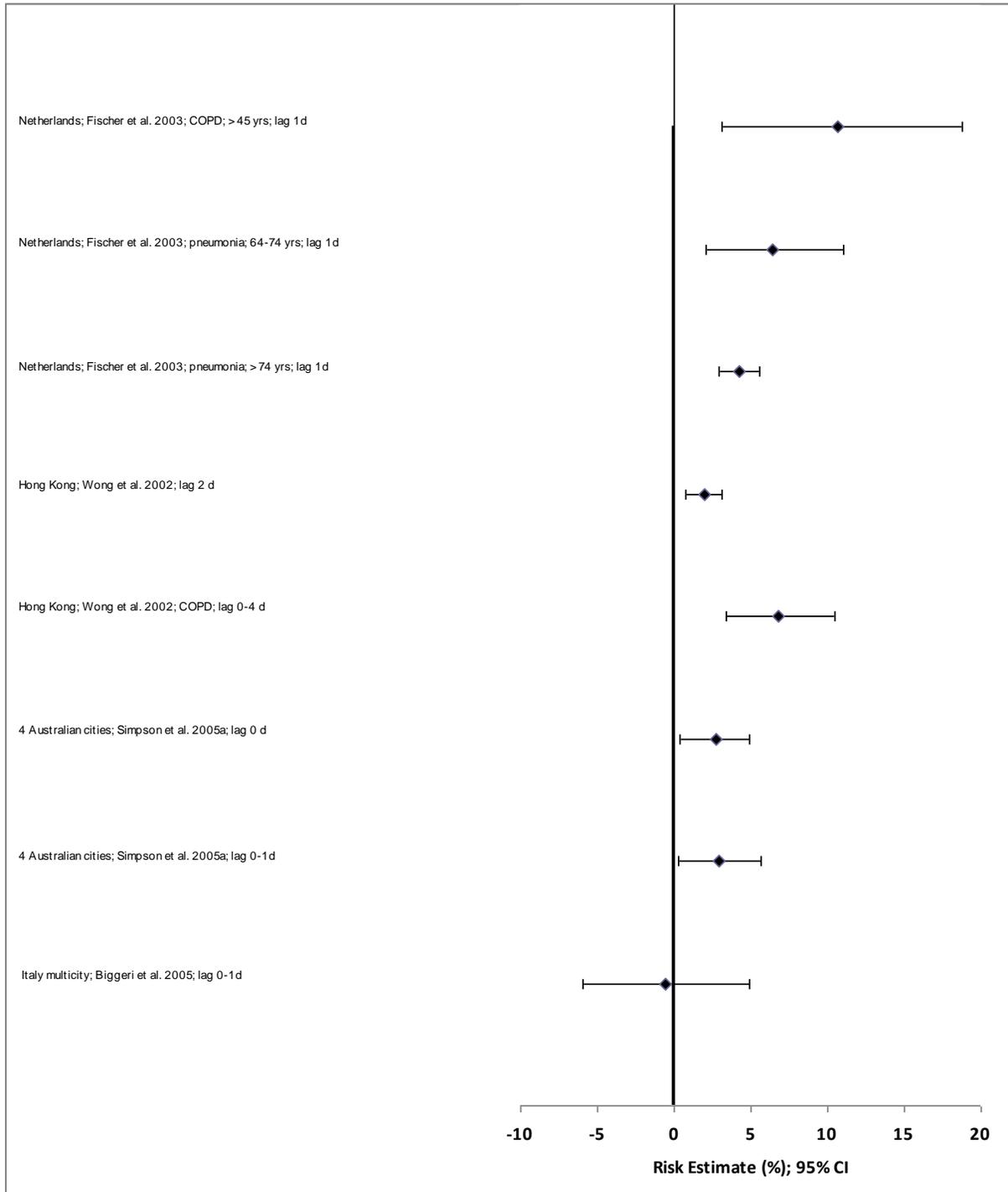
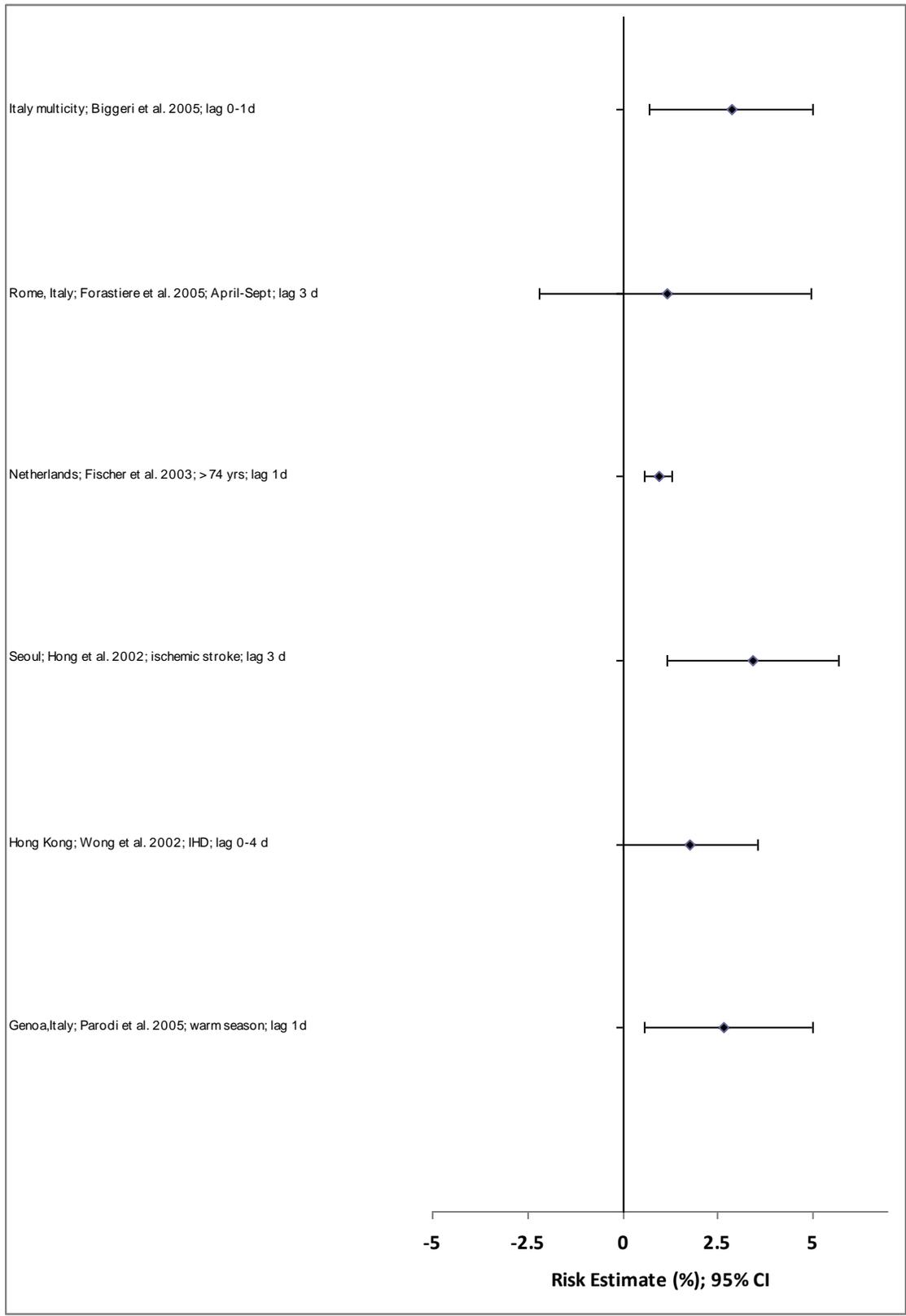


Figure 15.7 risk estimates for cardiovascular mortality per 10-ppb increase in 8-h ozone/6.7-ppb increase in 24-h ozone concentration in single-pollutant models



15.5.2 Hospital Admissions

Hospital admissions represent one of the key health indicators used to assess the effects of environmental factors such as air pollution on human health, since admissions data are collected and managed in standard databases. However, because these databases are often implemented for purposes other than public health surveillance, they may be limited by deficiencies that reduce their capacity to be used in epidemiological analyses. Generally, individuals who require hospitalization represent a small, but seriously ill, subset of all individuals who may be affected by air pollution. However, admissions are affected by a number of factors aside from the severity of morbidity, such as the availability of beds and the criteria for admission (which will vary between individual physicians and between health care systems). As a result, it can be anticipated that risk estimates for hospital admissions may be more heterogeneous and have greater variance than those for other health indicators, such as mortality.

15.5.2.1 Summary of Previous Assessments

The 1999 Ozone SAD reported that there was a strong and consistent relationship between ambient ozone and respiratory hospitalizations that was independent of other pollutants. Respiratory hospitalizations were increased by approximately 1% per 10 ppb daily 1-h max ozone in a number of meta-analyses or multi-city studies. This association was observed across studies conducted in locations differing in pollutant mixtures, components and population characteristics and employing differing statistical analyses. Respiratory hospitalizations increased in an ozone-concentration-dependent fashion, without showing an obvious threshold at concentrations as low as 20 ppb daily 1-h max ozone. At the time of this assessment, studies had just begun to examine the association between ozone and cardiovascular hospitalizations.

In 2006, the US EPA Ozone AQCD reported that ozone was associated with total respiratory, asthma and COPD hospital admissions in both single- and multi-city studies. These effects were stronger in the warm season than in the cold season. The greatest estimates of risk were usually associated with short lag periods (0 or 1 d), though risks were increased over several days in some studies. In most cases when other pollutants were considered, associations with ozone were robust to adjustment for co-pollutants, particularly PM. Finally, some evidence suggested that asthmatics and older adults may be at greater risk than other members of the population. Cardiovascular hospitalizations were increased in some studies, largely those where ozone levels were relatively high and during the warm season; however, the available evidence for admissions for cardiovascular causes was considered inconclusive.

15.5.2.2 Respiratory Admissions

Data from 1986 to 1999 were used in a case-crossover study of the associations between air pollution and hospital admissions for COPD and pneumonia among adults over the age of 65 in 36 US cities (Medina-Ramon et al., 2006). Mean 8-h ozone levels in the warm season ranged from 15.0 ppb in Honolulu, HI, to 63.0 ppb in Los Angeles, CA. A 10-ppb increase in daily 8-h mean ozone was associated with significantly increased risks of COPD admissions at lag 1 d: 0.66% (95% CI 0.38–0.94%) and 0.96% (95% CI 0.60–1.32%) for all-year and warm-season-only data, respectively. For pneumonia, a 10-ppb increase in ozone was associated with increased risks for pneumonia admissions at lag 1 d for all-year and warm-season data only: 0.42% (95% CI 0.22–0.60%) and 0.84% (95% CI 0.58–1.10%), respectively. Both categories of hospitalizations were more strongly associated with PM₁₀, but adjustment for PM₁₀ did not substantially modify the results (data not provided). The association of ozone with each of COPD and pneumonia was reduced in cities with a greater percentage of households with

central A/C, while that for COPD was reduced in cities with a greater variance of summer apparent temperature.

Simpson et al. (2005b) examined the relationship between daily measures of ozone and other pollutants and daily respiratory hospital admissions in four Australian cities from 1996 to 1999. Mean 1-h max ozone concentrations ranged from 24.4 to 33.8 ppb. At lag 3 d, total respiratory hospital admissions were increased significantly or marginally in Melbourne and Brisbane respectively, but not in Perth or Sydney (data in graph only). In the pooled analysis, significant associations were found for combined asthma and COPD admissions among adults ≥ 65 years of age at lag 0 and 3 d for a 10-ppb change in 4-h max ozone (1.31% (95% CI 0.10–2.63%) and 1.41% (95% CI 0.10–2.63%) respectively), and at lag 3 d for a 13.3-ppb change in 1-h max ozone (1.61% (95% CI 0.13–2.95%)). NO_2 and bsp were associated with hospitalizations from a wider range of causes, and generally the associations were stronger. In multi-pollutant models with NO_2 or bsp, ozone was not associated with respiratory admissions among adults ≥ 65 years of age.

Warm-season ozone was not associated with respiratory hospitalizations in a meta-analysis of data from four Italian cities from 1990 to 1999 conducted by Biggeri et al. (2005), but significant associations were reported for other pollutants (NO_2 , CO, PM_{10}). The authors indicated that increased between-city heterogeneity observed in models of hospital admissions compared with mortality may have been the result of differences in quality of reporting, filing criteria for admissions, and less access to hospital beds in the summer (fewer available beds being associated with lower admission rates and therefore smaller sample size).

Hinwood et al. (2006) used a time-stratified case-crossover design to examine the relationship between air pollution and respiratory hospitalizations in Perth, Australia, between 1992 and 1998. The average 1-h ozone concentration was 31.6 ± 10.2 ppb; ozone was not associated with respiratory, asthma, pneumonia or gastrointestinal disease admissions at any lag or ozone metric examined (effect estimates were often negative or near unity). Ozone generally was not associated with COPD admissions except for a decreased risk with 1-h average ozone at lag 1 d (-4.97% (95% CI -9.52 to -0.27%) per 13.3-ppb ozone change). A small number of significant associations were observed for CO, NO_2 and particles. Multi-pollutant models were not examined. It was noted that the general lack of significant associations may have been due to low statistical power owing to relatively few cases in some disease categories.

Farhat et al. (2005) assessed the relationship between air pollution and hospital admissions for bronchopneumonia, and asthma or bronchiolitis between 1996 and 1997 among children less than 13 years of age in Sao Paulo, Brazil. Mean hourly average ozone concentrations were $72.1 \pm 40.1 \mu\text{g}/\text{m}^3$ (36.05 ± 20.05 ppb). The data were analyzed with GAMs with LOESS smoothers without reporting the nature of the convergence criteria employed (default or stringent). A 10-ppb increase in ozone was associated with increased hospital admissions for pneumonia or bronchopneumonia combined using a 7-d moving average (approximately 8.11% (95% CI ~1.2%–16.63%)) and marginally associated with asthma or bronchiolitis hospital admissions combined using a 3-d moving average (~8.11% (95% CI ~-0.4–18.26%)) (data only presented in figures). Both categories of hospital admissions were also significantly increased in relation to PM_{10} , NO_2 , SO_2 and CO. In two-pollutant models, ozone was significantly associated with an increased risk of hospital admissions for pneumonia or bronchopneumonia when regressed with CO (7.87% (95% CI 0.16–19.4%)), but risk estimates for ozone in two-pollutant models with the other pollutants and for asthma or bronchiolitis admissions remained positive but were no longer statistically significant.

15.5.2.3 Cardiovascular Admissions

von Klot et al. (2005) studied a cohort of 22,006 adults over the age of 35 from five European cities who had survived a first MI. They tracked cardiac-related hospital readmissions in these individuals from 1992 to 2000 and studied the relationship between these admissions and air pollutants (daily 8-h max ozone ranged from 63.9 to 114.9 $\mu\text{g}/\text{m}^3$ (31.95–57.45 ppb)). A 10-ppb increase in daily 8-h max ozone was associated with increased admissions for angina pectoris (5.83% (95% CI 1.58–10.25%)) and all cardiac events (3.44% (95% CI 0.13–6.76%)), but not MI (0% (95% CI -6.01–6.36%)). The authors reported (data not presented) that results for ozone were similar in two-pollutant models with PM_{10} , PN, NO_2 and CO. All ozone analyses were restricted to the months of April to September. Significant associations were also observed with other pollutants (PM_{10} , PN, NO_2 and CO).

Ballester et al. (2006) examined the association between ozone exposure and cardiovascular and heart disease admissions in 14 Spanish cities between May and October from 1995 to 1999. Mean 8-h ozone concentrations ranged from 45.9 to 88.5 $\mu\text{g}/\text{m}^3$ (23.0–44.3 ppb). In pooled analyses a 10-ppb increase in ozone was associated with cardiovascular admissions (1.38% (95% CI 0.68–2.06%)) and heart disease admissions (1.32% (95% CI 0.20–2.42%)) with a 2–3 d moving average in single-pollutant models. These effects remained consistent in two-pollutant models with CO, NO_2 , particulates and SO_2 . Associations with other pollutants (PM, SO_2 , NO_2 and CO) were observed at earlier lags (0–1 d).

Simpson et al. (2005b) examined the relationship between ozone and daily cardiovascular hospital admissions in four Australian cities from 1996 to 1999 (details presented in Section 15.5.2.2, Respiratory Admissions). In single-city analyses, ozone was not significantly related to total daily cardiac admissions in any city, and most estimates were decreased. In the pooled analysis, a 10-ppb increase in 1-h or 4-h max ozone was not associated with cardiovascular hospital admissions, except for an increased risk among subjects 15–64 years old at a 3-d lag of 4-h max ozone (0.90% (95% CI 0.10–1.71%)) and a decreased risk for all ages for 0–1 d average ozone (-0.60% (95% CI -1.19 to -0.10%)).

In an Italian meta-analysis of data from four cities (details presented in Section 15.5.2.2) other pollutants (SO_2 , NO_2 , CO, PM_{10}), but not ozone (warm season only) were associated with cardiovascular hospitalizations; in fact, ozone was associated with a non-significantly decreased risk of admission from cardiac causes (Biggeri et al., 2005).

In a single-city Australian study, Hinwood et al. (2006) used a time-stratified case-crossover design to examine the relationship between air pollution and cardiovascular hospitalizations in Perth from 1992 to 1998 (details described in Section 15.5.2.2). It was observed that ozone was not significantly associated with cardiovascular admissions at any lag or ozone metric examined (odds ratios were all near unity). Significant associations with cardiovascular disease admissions were observed for CO and NO_2 . Multi-pollutant models were not examined.

15.5.2.4 Summary and Considerations: Hospital Admissions

Both the 1999 Ozone SAD and the US EPA 2006 Ozone AQCD reviewed research that studied widely differing locations, pollutant mixtures and populations, used various study designs, and concluded that ambient ozone was associated with respiratory hospital admissions. Increases were reported most often for total respiratory hospitalizations, but also included more specific categories, including admissions for COPD, asthma and pneumonia. Risks were usually greatest with same-day ozone or a 1-d lag, were often strongest in the warm season, and were often robust to adjustment for other pollutants, most often PM. These associations were linear down to relatively low concentrations, with no obvious threshold. In addition, older adults and asthmatics were identified as potentially susceptible populations. The results of more recent

studies reviewed in this assessment, though very limited in number and sometimes in design, provide some support for these earlier conclusions. In the stronger of these studies, exposure to ozone was associated with hospital admissions in older adults for COPD, pneumonia or asthma (Figure 15.8). Risks were most often greatest with very short lags, were more pronounced in the warm season than in all-year analyses, and most often remained increased (though not always significantly) after adjustment for co-pollutants. While weak or null findings were reported in the remaining studies identified, these studies were often limited by small sample sizes (number of cases or admission rates).

The US EPA 2006 Ozone AQCD concluded that there were positive associations between ambient ozone and cardiovascular hospital admissions in some studies, largely in the warm season. While ozone was not associated with cardiovascular hospitalizations across all the recently identified studies, results of two studies suggest that there were associations with warm-season ozone and that these associations were stable in multi-pollutant models (Figure 15.9). Furthermore, these two studies reported associations with both general admission categories (e.g. all cardiac events or cardiovascular admissions) as well as with disease-specific admissions (e.g. angina pectoris or heart disease admissions). Again, weak or null findings were reported in other studies reviewed; at least some of these were limited by small sample sizes (number of cases or admission rates)

In conclusion, earlier studies provide the strongest evidence for an association between ozone and respiratory hospital admissions. Recent studies, though few in number, provide some support for disease-specific admissions in older adults. Overall, there is less evidence for an association between ozone and cardiovascular admissions. However, when positive associations were observed between ozone and hospitalizations for subsets of CVD in the recent literature, these effects were significant in both single- and multi-pollutant models.

Figure 15.8 Risk estimates for respiratory hospitalization per 10-ppb increase in 8-h ozone/13.3-ppb increase in 1-h ozone concentration in single-pollutant models

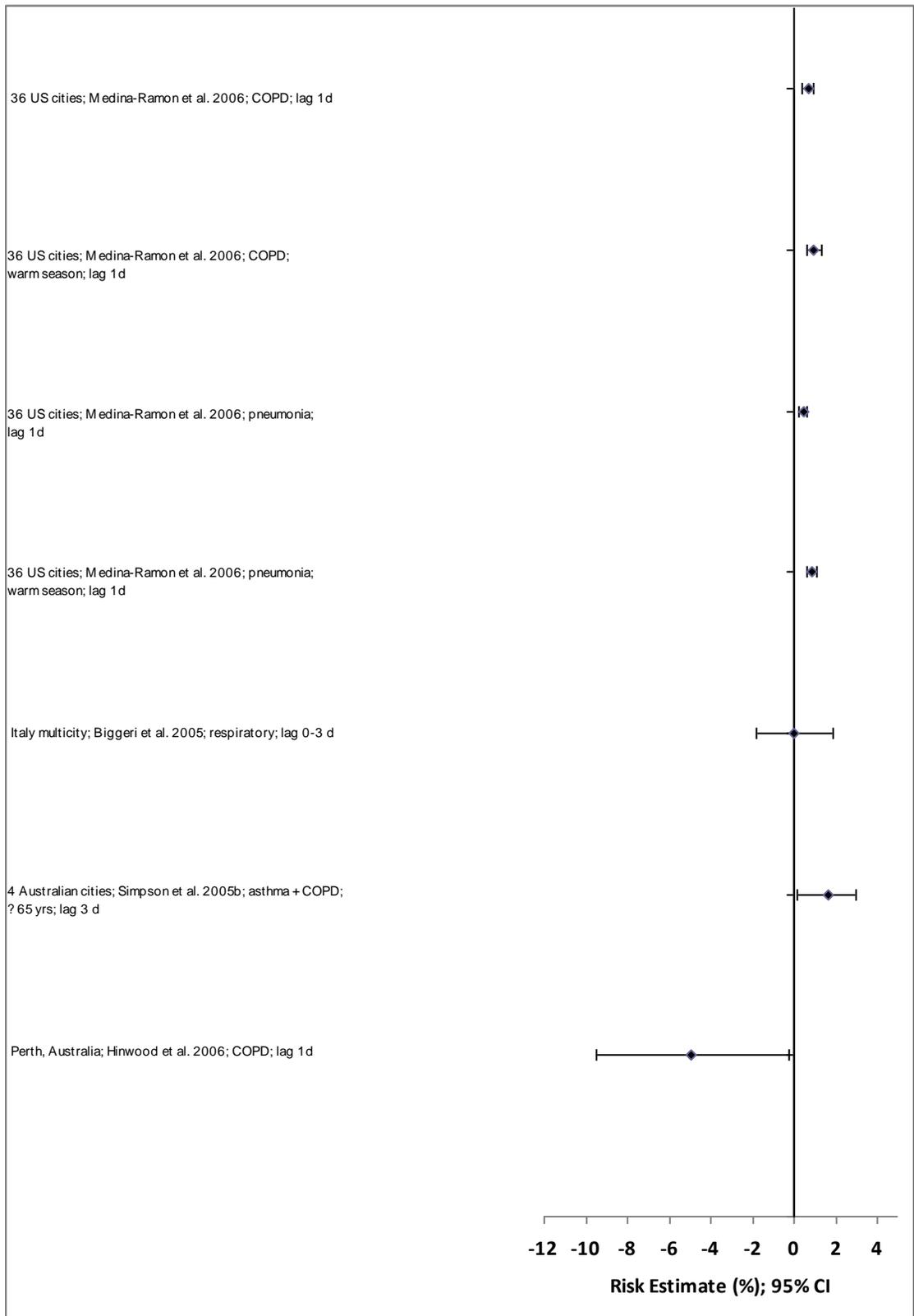
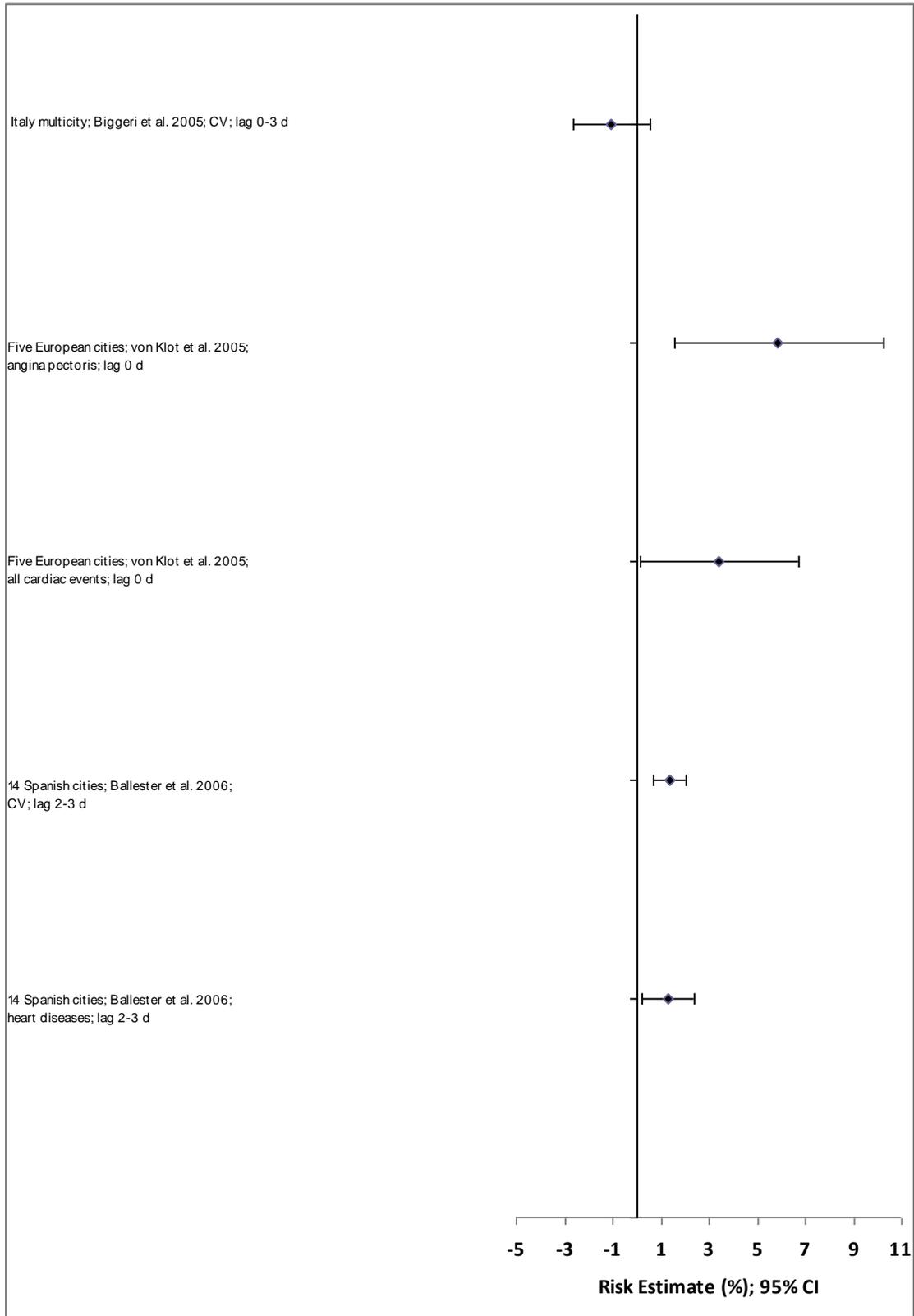


Figure 15.9 Risk estimates for cardiovascular hospitalization per 10-ppb increase in 8-h ozone concentration in single-pollutant models



15.5.3 Emergency Room Visits and Other Health Outcomes

With the use of administrative data records, ERVs provide a relatively objective and measurable indicator of the impact of ambient ozone on public health. Morbidities that result in ERVs are closely related to, but are generally less severe than, those that result in unscheduled hospital admissions. Medical visits (doctor's office visits, physician visits, general practitioner visits) are less studied but are also very relevant to assessing air pollution public health impacts.

15.5.3.1 Summary of Previous Assessments

At the time of the 1999 Ozone SAD, data on ERVs generally showed a positive association between ambient ozone and increased visits due to respiratory illness, principally for asthma, when cyclic variables, weather (in particular, temperature) and co-pollutants had been properly controlled for. An increase of about 6–8.6% in ERVs for asthma was predicted per 10 ppb increase in ozone (1-h max), usually lagged 1 or 2 d. The positive associations between ozone and emergency department respiratory visits, usually asthma, were observed in four different cities or metropolitan areas in three countries, including Canada. The mean summertime ozone levels (1–5 h metrics) varied between 30 and 90 ppb. No studies of other health outcomes were reported.

The US EPA 2006 Ozone AQCD reported that in a number of studies ozone was generally associated with asthma ERVs during the warm season, for which effect estimates tended to be positive and larger than results for cool-season or all-year analyses. Excess risks were mostly associated with short lag periods (0–2 d), and among the studies that reported a positive association between ambient ozone and ERVs for respiratory outcomes, ozone effects were generally found to be robust to adjustment for PM₁₀, NO₂, SO₂, and BS. However, some inconsistencies in ERV studies of ambient ozone were noted, which was attributed at least in part to differences in model specifications and analytical approach among the various studies. Evidence from two studies also suggested that ozone was associated with school absenteeism that was not attributable to other pollutants (PM₁₀ and CO or NO₂); however, it was concluded that further replication was required before firm conclusions could be reached.

15.5.3.2 Respiratory Emergency Room Visits

Boutin-Forzano et al. (2004) examined the relationship between air pollution (8-h average ozone 50.1 µg/m³ (25.05 ppb)) and ERVs for asthma, among individuals 3–49 years of age in Marseille, France, identified over a 1-year period. The investigators used a case-crossover design and logistic regression analysis, adjusting for meteorological variables. Only single-pollutant models were examined. A 10-ppb increase in ozone was associated with a significant increase in asthma-related ERVs at lag 0 d (1.22% (95% CI 0.12–3.12%)), lag 2 d (2.03% (95% CI 0.51–3.56%)), and lag 3 d (1.89% (95% CI 0.33–3.46%)). No associations were observed with NO₂ and SO₂.

Tobias et al. (2003) conducted a sensitivity analysis of model types used to analyze the relationship between ERVs for asthma and ozone and NO₂ (concentrations not reported). Both pollutants were modelled simultaneously and the study was conducted in Madrid, Spain, using data from 1995 to 1998. Linear, Poisson, overdispersed Poisson, autoregressive Poisson and GAMs were tested, controlling for long-term time trends, seasonality, temperature, humidity, weekdays, public holidays and acute respiratory infections. While individual lags from 0 to 4 d were investigated, only lag 1 d results were presented for ozone. Linear models were affected by residual autocorrelation and standard Poisson models by inadequate control for autocorrelation and overdispersion. The positive results for an association between ozone (lagged 1 d) and ERVs for asthma from an overdispersed Poisson model and Poisson autoregressive models were similar (adjusted regression coefficient beta = 4.4168, SE =

1.1398; and beta = 4.3366, SE = 1.3548). Likewise, results using GAMs with default convergence provided similar results to the latter two models, but with tighter SEs (beta = 1.5942, SE = 0.0957). In addition, somewhat greater effect estimates were observed using more stringent GAM convergence criteria compared with the default criteria. Therefore, the authors concluded that GAMs best fit the data with respect to autocorrelation and reduction of overdispersion. Results for NO₂ followed a similar pattern.

Between 1996 and 1997, Farhat et al. (2005) examined the relationship between air pollution and ERVs and hospital admissions for all lower respiratory diseases combined among children less than 13 years of age in Sao Paulo, Brazil. Based on the ICD codes described in the paper, these conditions included asthma, bronchiolitis, and pneumonia. GAMs with LOESS smoothers were used, but the nature of the convergence criteria employed was not reported. Mean hourly average ozone concentrations were $72.1 \pm 40.1 \mu\text{g}/\text{m}^3$ (36.05 ± 20.05 ppb) and an IQR increase in ozone ($49.3 \mu\text{g}/\text{m}^3$ (24.65 ppb)) was associated with increased ERVs for lower respiratory disease in single-pollutant models at a 4-d moving average (~5.68% (95% CI ~3.25–8.11%)). In co-pollutant models, ozone was associated with similar risks for increased lower respiratory disease ERVs with PM₁₀ (3.12% (95% CI 0.28–5.96%)), SO₂ (4.87% (95% CI 2.27–7.46%)), and CO (5.31% (95% CI 2.84–7.79%)); however, including NO₂ in two-pollutant models reduced the effect estimate for ozone (1.22% (95% CI -1.62–4.06%)). No associations were observed with ozone in multi-pollutant models. Effects were observed in one- and two-pollutant models with other pollutants (PM₁₀, NO₂, CO, SO₂ (negative association)), but only NO₂ was significantly associated with an increased risk of ERVs in a multi-pollutant model.

15.5.3.3 Cardiovascular Emergency Room Visits

Villeneuve et al. (2006a) conducted a time-stratified case-crossover study to explore the relationship between air pollution and ERVs for stroke (total, ischemic and hemorrhagic) in older adults (≥ 65 years of age) in Edmonton, AB, from 1992 to 2002. Single- and two-pollutant models were examined for lags 0 and 1 d and a 3-d average. The average daily mean ozone was 17.0 ± 9.1 ppb. While associations were observed with other gaseous pollutants (CO and NO₂), stroke ERVs were not associated with exposure to ozone during all seasons, cool months or warm months. Warm-season risk estimates were greatest but still non-significantly increased for acute ischemic stroke (lag 3 d, OR = 1.08 (95% CI 0.92–1.28)) and for hemorrhagic stroke (lag 3 d, OR = 1.11 (95% CI 0.89–1.38)).

Lin et al. (2003) conducted a study in Sao Paulo, Brazil, in 1994–1995 and reported a positive, non-significant association between a 5-d moving average of ozone and ERVs for ischemic cardiac diseases (angina and MI) in adults 45–80 years of age. The 24-h average ozone concentration was $58.80 \mu\text{g}/\text{m}^3$ (29.4 ppb). Both GAMs and GLMs were used, controlling for seasonal and weather factors using 0–7 d moving averages. A significant association was only observed with CO.

15.5.3.4 Other Health Outcomes (Physician Visits, Disability Days, School Absenteeism)

Villeneuve et al. (2006b) conducted a time-series study among older adults in Toronto, ON, between 1995 and 2000 but did not observe significant associations between air pollutants (O₃, NO₂, SO₂, CO, PM_{2.5} and PM₁₀) and physician visits for allergic rhinitis during any season. Numerical data were not presented, and no pattern was observed across effect estimates for single-day lags from 0 to 6 d; for example, the percentage change in physician visits was not consistently increased across the lags examined, nor was there consistency in lag-day-specific risk estimates among seasons or all-year analyses. GLMs were adjusted for seasonality, temperature, relative humidity, aeroallergens, overdispersion, serial correlation and calendar effects for lags from 0 to 6 d. The 8-h ozone concentration averaged 30.0 ± 15.4 ppb. In

contrast to the negative findings for pollutants, ragweed particulate levels were positively associated with the frequency of physician visits, and this risk was most pronounced for extended periods of high ragweed levels.

Stieb et al. (2002) examined the relationship between disability days and air pollution in Toronto, ON. Investigators used data (days spent in bed + days cut down on usual activity) from the first three cycles (1994–1995, 1996–1997, and 1998–1999) of Canada's National Population Health Survey, a biannual survey of the general health of Canadians. Data were available from 5,309 interviews. Time-series analysis using stepwise regression with GAMs and a LOESS smoother for weather variables was employed; in other analyses (not shown), using parametric natural spline functions of weather variables rather than the non-parametric smooths did not change the effect estimates. The mean 24-h ozone concentration in the 2 weeks prior to interviews was 19.2 ± 7.6 ppb. It was found that an IQR increase in ozone was not significantly associated with disability days, either for all-year or May–September data (point estimates were negative with large confidence intervals). The investigators stated that the inability to isolate restrictive activity days due to respiratory causes could account for the lack of an ozone effect. Significant increases in disability days were associated with CO and PM_{2.5}.

Park et al. (2002) examined the association between air pollution (8-h ozone averaged 22.86 ppb) and elementary school absenteeism in Seoul, South Korea. A time-series approach using GAM with LOESS smoothers was used (convergence criteria were not reported). A 10-ppb increase in 8-h average ozone was associated with a positive and linear increase in illness-related absences (4.95% (95% CI 3.72–6.77%)) but not total absences (0.63% (95% CI -0.63–1.87%)). Ozone was also associated with a decrease in non-illness-related absences (-10.36% (95% CI -13.06% to -8.37%)). The risk of illness-related absenteeism levelled off at ozone concentrations below about 20 ppb, suggesting a possible threshold for this effect. In two-pollutant models that included ozone and either SO₂ or PM₁₀, estimates were slightly greater than those obtained from the ozone-only model (6.16% (95% CI 4.34–7.97%) and 6.16% (95% CI 4.34–7.97%), respectively). Single-pollutant associations were also observed with PM₁₀ and SO₂, but not NO₂.

15.5.3.5 Summary and Considerations: Emergency Room Visits and Other Health Outcomes

The limited recent literature supports the previous conclusions of the 1999 Ozone SAD and the US EPA 2006 Ozone AQCD that acute exposure to ambient ozone is associated with increases in ERVs for asthma. All three of the studies reviewed in this assessment reported significant ozone-related increases, with short lags, in ERVs for asthma or for respiratory categories that would have included asthma. As in the literature reviewed in earlier assessments, these more recent studies were conducted in locations that would be expected to have differing pollutant mixtures (Europe and South America), and the risks of ozone-related ERVs were fairly robust to adjustment for various other pollutants or were not significantly related to other pollutants, indicating that they are specific to ozone.

The recent available data on other medical visits and related endpoints are too limited to draw any firm conclusions, both because the number of studies is so small and because they investigated such disparate health measures. In studies of cardiovascular endpoints, ambient ozone was not significantly related to ERVs for stroke in one study or for ischemic cardiac disease in another; both of these health outcomes were instead associated with other pollutants. In a study from Seoul, South Korea, ozone was associated with increases in illness-related school absences that were robust to adjustment for other pollutants, confirming findings for a small number of studies of school absenteeism reviewed in the US EPA 2006 Ozone AQCD. With respect to other health measures, ambient ozone was not associated with

physician visits for rhinitis or disability days in two Canadian studies that were reviewed in this assessment.

15.5.4 Panel Studies

Panel studies are epidemiological studies designed to examine groups of people engaged in normal activities in the natural environment, in which pollutant levels may be closely monitored and exposures are usually to the ambient mix of pollutants. These studies have the advantage that subjects of all ages and health status may be included. In addition, it is possible to track subjects' medical histories, episodes of illness, lifestyles and activity patterns. Endpoints are repeatedly measured and may include clinical, biochemical or physiological changes. Even with a small number of subjects, repeated measurements can maximize information and increase power and precision by decreasing the variability of intrasubject response (Delfino et al., 2002).

15.5.4.1 Summary of Previous Assessments

Of 20 panel studies reviewed in the 1999 Ozone SAD, 19 reported a significant association between acute exposure to ambient ozone and decreases in lung function and/or increases in symptoms and/or asthma medication use among both healthy and asthmatic adults and children. Most studies used single-pollutant models, but ozone-related effects remained significant after adjustment for PM or temperature in those studies that evaluated these factors. Outdoor workers and individuals who were exercising outdoors in summer had ozone-related reductions in lung function that systematically declined if exposures were repeated on consecutive days.

The US EPA 2006 Ozone AQCD included a review of the literature through the year 2004. Positive associations between ozone and decrements in lung function (FEV₁, FVC, PEF) were observed in a number of studies of children and asthmatic subjects, supporting the results of controlled human exposure studies that also suggested ozone was associated with reduced lung function. The results of panel studies also provided evidence for an association between ozone and increases in a wide range of respiratory symptoms and in as-needed asthma medication use in asthmatic children. Associations in healthy children were less robust. It was indicated that there was potential for respiratory effects to be greater with more time spent outdoors and higher levels of exertion in combination with increased exposure to ozone. Limited evidence suggested that acute exposure to ozone was associated with acute inflammation of the upper airways in children. Ozone was associated with the generation of ·OH radicals, and antioxidants were shown to decrease the effects of ozone in outdoor workers and in children with moderate to severe asthma. A very small number of panel studies of the effects of ozone on cardiovascular endpoints provided limited but suggestive evidence of a potential effect on HRV, ventricular arrhythmias and MI incidence.

15.5.4.2 Respiratory Effects

Schildcrout et al. (2006) conducted a multi-city North American study of the relation between ambient air pollutants and asthma exacerbation among 990 CAMP participants (data collected daily during the 22-month pre-randomization phase of this clinical trial of asthma management in children). No significant associations were observed between ozone (median 1-h max: 55.0 ppb) and asthma symptoms or rescue inhaler use (e.g. RR = 1.06 (95% CI 0.92–1.23) and RR = 1.01 (95% CI 0.92–1.10) per 30 ppb 1-h max ozone at lag 0 d, respectively) during the summer months (May–September 1994–1995). The authors reported, however, that it was difficult to observe warm-season ozone effects (the only effects considered) because only a small number of subjects were sampled each day (approximately 12 per city). This restricted the analysis so

that ozone exposures could not be applied to all possible subjects studied over all possible years. Associations were observed with other gaseous pollutants (NO₂, CO, SO₂) but not PM₁₀.

Delfino et al. (2002) conducted a study among children in California over a 2-month period, March and April 1996. Ozone (mean 1-h max 69 ± 16 ppb; mean 8-h max 60 ± 12 ppb) was positively, but either marginally or not significantly associated with asthma symptoms (aggregate of cough, wheezing, sputum production, shortness of breath and chest tightness) (OR = 3.27 (95% CI 1.00–10.7) per 43-ppb 1-h max ozone; OR = 2.72 (95% CI 0.67–11.0) per 36-ppb 8-h max ozone). The magnitude of effect estimates was greater in subjects not on medication. In addition, in sensitivity analyses ORs decreased when the top 5% of 1-h max ozone concentrations were dropped, suggesting that effects may be attributable to a few days with elevated ozone concentrations. The authors stated, however, that this analysis was exploratory and further work is required to model and describe the exposure–response curve. Associations were observed with other pollutants (NO₂, PM₁₀) and fungi, and when ozone was regressed in two-pollutant models with NO₂ or PM₁₀, declines in the ozone estimate were greater than for any co-pollutant.

Rabinovitch et al. (2004) conducted a study among asthmatic children (most with moderate to severe asthma) in Denver, CO, followed daily over three consecutive winters. The authors concluded that ozone (daily 1-h max averaged 28.2 ppb) was not associated with any significant clinical outcomes (results for medication use, FEV₁, PEF, day- and nighttime asthma symptoms, and asthma exacerbations were not reported or were non-significant and in the opposite direction to what was expected). A small increase in current-day asthma symptoms was the only significant result presented for ozone (OR = 1.083 (95% CI 1.002–1.170) per 11.4-ppb ozone). However, the authors also stated that they could not rule out chronic effects or effects at higher concentrations of ozone. Ozone levels were negatively correlated with other pollutants (data not shown). No significant associations were observed with other pollutants (SO₂, NO₂, CO, PM₁₀ or PM_{2.5}), except for a marginally significant increase in daily use of bronchodilators in relation to CO.

Peacock et al. (2003) examined the association between ozone and respiratory function among a group of British children during the winter months (November 1996–February 1997); 1-h maximum ozone concentrations averaged 25.8 ± 11.1 ppb. Ozone was not associated with reduced respiratory function at lag 2 d (OR for a 20% decrement in PEF below the median = 0.987 (95% CI 0.975–0.998) per 1-ppb 1-h max ozone, and OR = 0.981 (95% CI 0.968–0.995) per 1-ppb 8-h max moving average ozone) and with a 5-d average (1-h max). NO₂ and PM₁₀ were associated with significantly increased odds of reduced lung function.

Triche et al. (2006) conducted a study in southwestern Virginia among infants followed for approximately 83 d in summer (June–August) 1995 and/or 1996. Significant effects of ozone on wheezing and difficulty breathing were observed among infants whose mothers had asthma, with the strongest effects observed with 24-h ozone levels (average: 35.2 ± 8.4 ppb) (OR_{wheeze} = 1.65 (95% CI 1.01–2.70); OR_{difficulty breathing} = 2.14 (95% CI 1.42–3.20) per 11.8-ppb ozone). In multi-pollutant models with PM_{2.5} and PM_{10–2.5}, similar results were observed, with the addition of some positive, significant effects on wheezing in all infants. No data were reported for PM₁₀ or PM_{10–2.5}, although ozone was moderately correlated with PM_{2.5}. The authors concluded that at ambient ozone levels, infants (particularly those whose mothers are asthmatics) are at increased risk of respiratory symptoms.

Lagorio et al. (2006) examined the impact of air pollutants on respiratory function among older adults with IHD, asthma, or COPD in Rome, Italy, over the spring (May–June) and winter (November–December) seasons. Ozone (24-h average: 42.6 ± 29.5 µg/m³ (21.3 ± 14.8 ppb)) was not associated with changes in FVC or FEV₁ in any of the three panels. However, there

were significant associations with PM_{2.5}, PM_{2.5}-metals and NO₂ in the COPD panel, and with NO₂ in the asthma panel.

Girardot et al. (2006) conducted a study of adult hikers in the eastern US during August–October 2002 and June–August 2003. Ozone (daily average: 48.1 ± 12.0 ppb) was not associated with changes in lung function measurements (pre- vs. post-hike). This was in contrast to the findings of a similar earlier study conducted in same region (Korrick et al., 1998). The authors of the more recent study suggested that the differences between the studies may have been due to variability in spirometry coaching techniques, the age of the subjects (average of 46 years vs. 35 years in the earlier study) and the duration of exercise (5.0 h vs. 8.0 h in the earlier study). No effects were associated with PM_{2.5}.

In Mexico City (mean 8-h max ozone moving average: 69 ± 31 ppb), 52 asthmatic children participating in an antioxidant vitamin supplementation study were genotyped. Symptoms (cough and difficulty breathing) and bronchodilator use associated with exposure to ozone were stronger in subjects with GSTM1 *null* and GSTP1 *Val/Val* genotypes, with evidence of an even greater effect in subjects with both of these genotypes. GSTs are involved in the metabolism of reactive oxygen species. No changes in lung function were observed in any subjects, which the authors suggested might have been due to the limited sample size (Romieu et al., 2006).

In two European studies that were limited by methodology or reporting, associations were observed between ambient ozone and respiratory symptoms in schoolchildren (Zeghnoun et al., 2003; Steerenberg et al., 2003).

In two studies from settings that are considered of uncertain relevance to Canada, no associations between ozone and PEF or respiratory symptoms were observed in a study of street vendors in Bangkok, Thailand, or a study of the effects of Asian dust storms in Korea (Kongtip et al., 2006; Park et al., 2005).

15.5.4.3 Effects on Biological Markers

In comparison with controlled human exposure (clinical) or toxicological studies, very few of the panel studies that were reviewed investigated the effects of ozone on changes in biological markers.

Dubowsky et al. (2006) conducted a study among older adults as they participated in four monthly diesel-powered bus trips in St. Louis, MO. The mean 24-h average ozone concentration was 24 ± 9.4 ppb. In subjects with diabetes, obesity and hypertension a 7.2-ppb increase in the 5-d moving average of ozone was associated with elevated levels of two inflammatory markers, CRP and IL-6: increases were 41% (95% CI 7.6–84%) and 22% (95% CI 1.9–45%), respectively. An inverse association between ozone and WBCs was non-significant and was inconsistent, with positive associations being observed with other pollutants (data not presented). Positive, often significant, associations with various of these inflammatory markers were also observed with PM_{2.5}, BC, NO₂ and CO.

Other studies presented limited data with respect to results for ozone, because they were focused principally on other pollutants, most often PM. Delfino et al. (2006) conducted a study among asthmatic adolescents in California, but ozone was not associated (data not shown) with significant changes in FeNO (average 8-h max ozone levels in two locations were 76.37 ± 18.47 ppb and 40.56 ± 14.12 ppb, respectively). However, significant effects were reported for PM_{2.5}, EC, OC and NO₂. Likewise, Lagorio et al (2006) reported that they did not observe a significant relationship between FeNO in older asthmatic adults in Rome, Italy, and several air pollutants including ozone (no data were reported) (24-h average ozone was 42.6 ± 29.5 µg/m³ (21.3 ± 14.75 ppb)). Finally, associations were not detected between ozone and urinary CC16 concentrations (a protein specific to the lung epithelium secreted in the respiratory tract by

nonciliated Clara cells, used as a marker for lung damage) in two-pollutant models in an ULTRA project study of older adults with CHD in three European studies (Timonen et al., 2004). Associations were observed with PM_{2.5} but not UFPs, NO₂ or CO.

15.5.4.4 Cardiovascular Effects

The cardiovascular effects of ozone were investigated in several recent panel studies by evaluating a variety of endpoints, including arrhythmias, ectopy (extra heartbeats), and HRV.

Rich et al. (2006a) studied paroxysmal atrial fibrillations measured by ICD discharges recorded between 1995 and 2002 in 29 older male and female subjects from Boston, MA. The only significant association was with hourly ozone (1-h median 22.2 ppb) at lag 0 h (OR = 2.08 (95% CI 1.22–3.54) per 21.7-ppb ozone); however, a positive association was also associated with hourly ozone at lag 0–23 h (OR = 1.60 (95% CI 0.89–2.89) per 15.8-ppb ozone). This was consistent across warm and cold months. No associations were observed with other pollutants (e.g. PM_{2.5}, BC, NO₂, SO₂ or CO). The authors suggested that the difference in significant lags between this study and earlier studies of ventricular arrhythmias indicated a more rapid response to air pollution with paroxysmal atrial fibrillation than ventricular arrhythmias. Overall, they concluded that community air pollution, rather than specifically ozone, was a factor for paroxysmal atrial fibrillation, suggesting that a larger sample of events was required to draw conclusions about specific pollutants.

Using the same window of data collection (July 1995–July 2002), no associations were observed between ventricular arrhythmias and ozone in all subjects (n = 203) in Boston, MA (Dockery et al., 2005). In subjects exposed to the upper quintile of ozone (35 ppb), the risk of a ventricular arrhythmia when a previous arrhythmia had occurred ≤3 d was significant (p < 0.05). No significant effects were observed at other quintiles. In categorical analyses with other pollutants, findings were stronger (PM_{2.5}, BC, CO) or similar (NO₂, SO₂). In another study of subjects with ICDs (n = 56) from St. Louis, MO, followed for approximately 1.5 years, a positive but non-significant association was observed between ambient ozone (24-h median 21 ppb) and ventricular arrhythmias (OR = 1.15 (95% CI 0.61–2.18) per 18-ppb ozone) for lag 0–23 h (Rich et al., 2006b). Greater ORs were observed with SO₂, NO₂ and EC, though only SO₂ was significant.

Sarnat et al. (2006a) examined the association between ozone and ectopy among predominantly female residents of Steubenville, OH, from June–August and September–December. The 24-h average concentration of ozone was 21.8 ± 12.6 ppb and the 5-d average was 22.2 ± 9.1 ppb. Supraventricular ectopy was non-significantly, positively associated with an increase of 14.9 ppb of ozone (5-d moving average) in one- (OR = 1.78 (95% CI 0.95–3.35)) and two-pollutant models with sulphate (OR = 1.57 (95% CI 0.74–3.35)). This association was weaker when a 24-h measure of ozone was used. Both PM_{2.5} and SO₄²⁻ were associated with significant effects, while non-significant associations were observed with EC, NO₂, SO₂ and CO.

Lipsett et al. (2006) examined the relationship between ozone and HRV among older adults with coronary artery disease in the Coachella Valley, CA. Mean 1-h max ozone levels were 33 ppb and 41 ppb at two fixed sites. Ozone measured 1 h before HRV measurements was non-significantly associated with decreased HF (p = 0.09). The average ozone concentration in the prior 8 h was also non-significantly associated with reductions in total power (p = 0.10) and LF (p = 0.08). Significant associations with several HRV variables were observed for PM₁₀ and PM_{10-2.5}.

A study of older adult subjects in Steubenville, OH, during summer and fall (1-h average ozone: 27.3 ppb) also failed to observe a significant association between ozone and HRV (Luttmann-Gibson et al., 2006). Specifically, the following associations were reported for a 16.4-ppb

change in ozone on the previous day: SDNN (-1.1% (95% CI -4.2–2.1%)), RMSSD (-2.5% (95% CI -8.4–3.9%)), HF (-3.8% (95% CI -14.9–8.7%)), LF (-3.9% (95% CI -14.2–7.6%)), and heart rate (0.7% (95% CI -0.3–1.6%)). Likewise, a study of 37 elderly subjects with coronary artery disease in the three European cities of the ULTRA project reported no associations between ozone and HRV in two-pollutant models (no ozone data presented and ozone not assessed in one-pollutant models) (Timonen et al., 2006). In the latter two studies, PM_{2.5} and other gaseous pollutants were associated with HRV parameters (Luttmann-Gibson et al., 2006; Timonen et al., 2006).

Park et al. (2006) studied a cohort of older adult male subjects from the VA Normative Aging Study (2000–04) in Boston, MA. This study of gene–environment interactions found similar non-significant declines in HRV associated with exposure to ozone across variants of HFE, which has a role in modulating Fe uptake. SDNN, HF, LF and LF/HF were all negatively related to ambient ozone, and percentage changes were similar regardless of HFE genotype, but the only statistically significant finding was with log₁₀ LF in subjects genotyped HFE wild-type (-19.5% (95% CI -32.0% to -4.7%) per 16-ppb ozone). PM_{2.5} was significantly related to a decrease in all HRV components, and the association in the HF component was restricted to persons with the wild-type genotype.

Zanobetti et al. (2004) reported that 120-h average ozone (mean 24 ppb) was significantly related to increased resting diastolic blood pressure among older adult subjects from Boston with CVD (2.7% (95% CI 0.02–5.4%)); associations with BC, SO₂ and PM_{2.5} were also observed. However, only that with PM_{2.5} remained significant in multiple-pollutant models (results not shown).

In two studies from Taiwan, no associations were observed between ozone and heart rate or blood pressure (Chuang et al., 2005) or HRV (Chan et al. 2005) (1-h average ozone concentrations were 22.4 ± 20.0 ppb and 21.9 ± 15.4 ppb, respectively). Instead, these cardiovascular endpoints were associated with other common air pollutants in both studies.

15.5.4.5 Summary and Considerations: Panel Studies

A significant number of panel studies of the health effects of ambient ozone were published in the review period and are summarized in this assessment. These studies have sometimes focused on health endpoints that have not been much investigated in the literature considered in earlier assessments. In addition, a number of the newer studies have been designed to examine the health effects of air pollutants other than ozone; therefore, the endpoints studied and/or the reporting are sometimes less informative with respect to the potential health effects associated with ozone. As a consequence, the extent to which newer findings support the conclusions of previous assessments of panel studies varies among the categories of health effects.

For example, previous assessments concluded that there were consistent ozone-related decreases in measures of lung function in healthy and asthmatic adults and children in numerous studies. These decrements were robust to adjustment for co-pollutants, most often PM. In addition, respiratory effects were reported in outdoor workers and individuals who were exercising outdoors in summer, groups that should be considered vulnerable to the respiratory health effects of ozone. Contrary to these earlier findings, there is little supporting evidence for ozone-related decrements in lung function in the more recent studies reviewed. However, several of these studies were conducted in the winter season, when time spent indoors in settings with relatively low air exchange would have increased exposure measurement error. As well, some of these studies did not find associations for other pollutants that have previously been linked to reduced lung function, which raises questions concerning the studies' ability to detect an effect of air pollution on this endpoint.

In contrast, the results of the studies reviewed in this assessment provide considerable evidence that ambient ozone is linked to increases in respiratory symptoms, confirming the findings of previous assessments. In all of the studies reviewed, which were conducted in the US and in Europe, ambient ozone was associated with increased risks of asthma symptoms in panels of children, most often asthmatics. In addition, in some, but not all, of these studies, the increase in ozone-related symptoms was robust to adjustment for other pollutants. The evidence that ozone is associated with increased asthma medication use is more variable, perhaps as a consequence of differences between studies in the severity of asthma, related differences in the use of maintenance versus rescue medication, and the conduct of some studies in the non-ozone season.

The evidence from panel studies linking ozone to effects on biological markers of exposure/effect is extremely limited. Ozone was associated with increases in markers of systemic inflammation in elderly bus riders in one study; this effect was only observed in the subset of subjects with diabetes, obesity and hypertension. In other studies, exposure to ambient ozone was not linked to biomarkers of airway inflammation (FeNO) or pulmonary damage (urinary CC16).

The US EPA 2006 Ozone AQCD concluded that there was limited but suggestive evidence from panel studies for the effects of ozone on cardiovascular endpoints, including HRV, ventricular arrhythmias and incidence of MI. In the recent literature there was some evidence that ozone was positively associated with heart arrhythmias (paroxysmal atrial fibrillation), supraventricular ectopy and HRV. However, the number of studies of these endpoints is limited, null findings for related endpoints were also reported in some studies, and findings were sometimes more strongly related to other common air pollutants. In addition, some positive findings were attributed to the general mixture of air pollution and not to specific pollutants by some authors. Therefore, the overall evidence for associations between ozone and changes in cardiovascular parameters remains limited.

One area in which the recent literature has contributed new information is in the study of differences in subgroups of the population. For example, the effects of ozone in subjects with diabetes, obesity, hypertension, IHD, asthma or COPD were studied, as well as the differences between infants with or without an asthmatic mother. The limited number of identified studies and the null findings reported in some studies preclude drawing any new conclusions with respect to subgroup sensitivity at this time, though there is some suggestion across this variety of conditions that inflammatory diseases may predispose individuals to be susceptible to the effects of ozone. The sensitivity of asthmatics to exposure to ozone has been well-documented in previous assessments.

15.6 Epidemiology Studies of Developmental and Reproductive Endpoints

Potentially adverse birth outcomes and reproductive effects resulting from exposure to air pollution have only recently been investigated. Several hypotheses have been proposed for the biological mechanisms that may underlie air pollution-related changes in birth outcomes. The theories include changes to the pituitary–adrenocortico–placental system, changes in uterine blood flow, maternal infections, abnormal placental development, acute and chronic inflammation, decreased supplies of oxygen and nutrients to the placenta, DNA damage, and oxidative stress. These mechanisms may interact or may even be causally interrelated.

15.6.1 Summary of Previous Assessments

At the time of the 1999 Ozone SAD there were no published studies on the effects of air pollution on birth outcomes or reproductive endpoints. In the US EPA 2006 Ozone AQCD a small number of studies were reviewed that examined the relationship between air pollutants including ozone and several birth outcomes, including intrauterine and infant mortality, premature birth and LBW (<2500 g). In these studies, ambient ozone was generally not convincingly associated with such birth outcomes (though an increased risk of LBW was related to third trimester ozone in a Korean study). Instead, these outcomes were most often associated with air pollutants that tend to peak in winter and are possibly traffic-related, most often CO but also NO₂, SO₂ and PM. Since most of these studies did not analyze the data by season, and several of these pollutants (including ozone) are strongly seasonal, it was observed that seasonal confounding may have influenced the reported associations. A suggestive association between ambient ozone concentrations in the second month of pregnancy and various heart vessel defects was reported in one study. Overall, the very limited database reviewed did not provide substantive evidence for any effects of ozone on birth outcomes.

15.6.2 Birth Outcome Endpoints

15.6.2.1 Infant Mortality

In the limited recent literature there were no clear associations between ambient ozone and SIDS or infant mortality. In a study of 12 Canadian cities between 1984 and 1999, ozone (mean 24-h average: 31.77 ppb) was not associated with an increased risk of SIDS (ozone data not presented), though NO₂ and SO₂ were significantly associated with the incidence of SIDS after adjusting for meteorological and seasonal indicator variables (Dales et al., 2004). In a California study, an apparent significant protective effect of ozone (mean 1-h average ~20 ppb) on all-cause infant mortality and on SIDS was observed in single-pollutant models (OR = 0.93 (95% CI 0.89–0.97) and OR = 0.89 (95% CI 0.82–0.96), respectively, per 1 pphm (10 ppb) ozone). Similar results were observed when data were stratified based on the ozone IQR (25th to >75th percentile and ≥75th percentile). These associations became non-significant in the majority of multi-pollutant models. Significant increases in mortality were associated with exposure to CO, NO₂ and PM₁₀ (Ritz et al., 2006).

15.6.2.2 Birth Weight

Several recent studies investigated associations between ambient ozone and LBW or declines in birth weight. All recent birth weight studies (published since the cut-off date for the US EPA

2006 Ozone AQCD) accounted for parity, maternal age and gender. In addition, several studies adjusted for season, race or ethnicity, parental education level, SES and gestational age.

In two Canadian studies, non-significant associations between ozone and increased risk of LBW were observed. In infants born between 1998 and 2000 in Nova Scotia, no associations between ozone (24-h average: 21 ppb) and risk of LBW were observed after adjusting for birth year (RR = 0.98 (95% CI 0.86–1.12), RR = 1.04 (95% CI 0.91–1.18) and RR = 1.01 (95% CI 0.88–1.16) per 7 ppb ozone in the first, second and third trimesters respectively). Comparable results were observed when data were stratified by quartiles of exposure (Dugandzic et al., 2006). Similarly, in infants born between 1985 and 1998 in Vancouver, BC, where the mean 24-h average for ozone was 13.4 ppb, no significant association was observed between a 10-ppb increase in ozone and risk of LBW in the first (OR = 1.04 (95% CI 0.95–1.13)) or last (OR = 1.01 (95% CI 0.92–1.11)) month of pregnancy (Liu et al., 2003). In both studies SO₂ was associated with an increased risk of LBW.

In a California (1994–2000) case-control study (2,778 of 136,134 term births were cases) where the mean 24-h average ozone concentration was 21.5 ppb, no association between ozone and term LBW was observed in the third trimester after adjusting for CO and/or PM₁₀ (data not presented). Significant associations were observed with CO and PM₁₀ (Wilhelm and Ritz, 2005). In an earlier study (1994–1996) (3,771 cases and 26,351 controls randomly selected from term births in the same year) by the same authors, annual ozone concentrations at the nearest monitoring station (IQR = 6 ppb) were not associated with term LBW (OR = 0.95 (95% CI 0.80–1.13) per 1 pphm (10 ppb) annual average ozone concentration). Concentrations of CO, but not PM₁₀ and NO₂ were significantly associated with term LBW (Wilhelm and Ritz, 2003). However, the focus of this study was not individual pollutant effects, but the relation of DWTD to LBW and preterm birth; the annual average exposure metric may be less relevant, as levels of ozone and some of these other pollutants display strong seasonal patterns.

In a study of infants born in California between 1975 and 1987 (a subgroup of participants from the CHS), ozone over the entire pregnancy (mean 24-h average: 27.3 ± 8.7 ppb) was marginally associated with LBW (OR = 1.3 (95% CI 0.9–1.8) per 12 ppb 24-h average ozone; and OR = 1.5 (95% CI 0.9–2.3) per 26 ppb 8-h average ozone). When data were stratified by trimester, third trimester results were also marginally significant for 24-h average ozone (OR = 1.4 (95% CI 1.0–1.9) per 17 ppb ozone) and significant for 8-h average ozone (OR = 1.4 (95% CI 1.1–1.9) per 33 ppb ozone). CO was associated with a significantly increased risk of LBW in the first trimester only. More robust findings were reported for reductions in mean birth weight, rather than categorical analyses using LBW. Over the entire pregnancy, as well as second and third trimesters, 24-h average ozone was associated with reductions in mean birth weight of -47.2 g (95% CI -67.0 to -27.4 g), -32.1 g (95% CI -50.7 to -13.4 g), and -35.2 g (95% CI -54.6 to -15.8 g), respectively; significant results were also reported for 8-h average ozone. Most of these findings were still significant, in addition to a significant finding in the first trimester with 24-h ozone, in sensitivity analyses with additional adjustments for temperature, elevation and season of birth. In two-pollutant models the first trimester effect on mean body weight for ozone was greater but still marginally non-significant in models with CO, but the third trimester effect remained when regressed with PM₁₀. When exposures to ozone during all three trimesters were modelled together only the third trimester effect was significant (24-h average only). A dose-response effect was observed across the upper four deciles of 24-h ozone exposure (>30 ppb) when each upper decile was compared with the lowest decile. While this result may suggest the presence of a threshold, the authors cautioned that further research was required before drawing any conclusions. In addition to the significant findings for ozone, there were also associations between PM₁₀ (third trimester) and CO (first trimester), but not NO₂, and declines in mean birth weight, though these were mostly smaller in magnitude (Salam et al., 2005).

The results from an Australian study conducted in Sydney initially suggested that there was a significant association between ozone (mean 1-h max: 31.6 ± 14.6 ppb) during the second trimester and declines in birth weight (-0.75 g (95% CI -1.38 to -0.12 g) per 1 ppb ozone), but this effect became significant in the opposite direction when data were restricted to women living within 5 km of a monitor (8.77 g (95% CI 1.05 – 16.49 g)), analyzed in a two-pollutant model with PM_{10} (18.28 g (95% CI 10.03 – 26.53 g)) or controlled for pollutant exposures during other pregnancy periods (8.84 g (95% CI 1.10 – 16.58 g)). In other analyses CO, NO_2 , PM_{10} and $PM_{2.5}$ were associated with declines in birth weight (Mannes et al., 2005).

In Taiwan, ambient ozone was marginally, but not significantly associated with an increased risk of LBW in a study of two cities with very different concentrations of ozone (24-h average: 16–20 ppb vs. 41–48 ppb). While the findings were not significant, there appeared to be a concentration–response relationship (comparing the lowest quartile of ozone concentrations with higher quartiles) in the third trimester and across the entire pregnancy. Significant associations were observed at high SO_2 concentrations (Lin CM et al., 2004).

15.6.2.3 Small for Gestational Age and Intrauterine Growth Reduction

SGA or IUGR cases were evaluated in a small number of studies. All studies controlled for parity, maternal age, gender and season.

The term IUGR refers to diminished fetal growth rates as a result of conditions in which a fetus is unable to achieve its genetically determined potential size, and while similar, is not the same as SGA. In a Canadian study in Vancouver, BC, (mean 24-h average: 13.4 ppb) ozone was marginally associated with IUGR in the first and second trimester (OR = 1.02 (95% CI 0.95–1.08), and OR = 1.08 (95% CI 1.01–1.15), respectively, per 10 ppb ozone), but risk estimates during the first and last month and third trimester of pregnancy were not significant (OR estimates near unity). Similar associations were also reported for other pollutants (SO_2 , NO_2 , CO), though these were restricted to the first month and first trimester of pregnancy (Liu et al., 2003).

In a study of infants born in California, who were a subset of subjects from the CHS born between 1975 and 1987 (585 of 3,901 had IUGR), ORs for ozone were significantly increased for the entire pregnancy and for the third trimester (OR = 1.2 (95% CI 1.0–1.5) per 26 ppb 8-h ozone, and OR = 1.2 (95% CI 1.0–1.3) per 33 ppb 8-h ozone, respectively), and were non-significantly increased in the second trimester (OR = 1.1 (95% CI 1.0–1.2) per 29 ppb 8-h ozone). ORs were virtually identical in analyses based on 24-h ozone. For CO, the risk for IUGR was significantly increased in the first trimester only, while there were no significant associations with NO_2 , or PM_{10} for any period. The mean 24-h average of ozone was 27.3 ± 8.7 ppb (Salam et al., 2005).

In an Australian study, there was a small but significantly increased risk of SGA associated with ozone in the second trimester (OR = 1.01 (95% CI 1.00–1.01) per 1 ppb 1-h max ozone). However, ORs were not increased in analyses restricted to babies born to women residing within 5 km of an air monitoring station (mean 1-h max: 31.6 ± 14.6 ppb). Stronger associations were observed with PM_{10} , $PM_{2.5}$ and NO_2 , particularly in babies born to women residing within 5 km of an air monitoring station (Mannes et al., 2005).

15.6.2.4 Premature (Preterm) Births

All recent studies that investigated premature births controlled for parity, maternal age, gender and season. In addition, in three of four studies adjustments were also made for race or ethnicity and level of prenatal care. In a study conducted in Vancouver, BC, the mean 24-h

average of ozone was 13.4 ppb; a 10.0-ppb increase in ozone was associated with a non-significant decreased risk of preterm birth in the first and last months of pregnancy (OR = 0.98 (95% CI 0.89–1.03) and OR = 0.93 (95% CI 0.86–1.00), respectively). Both CO and SO₂ were associated with a significantly increased risk of preterm birth in the last month of pregnancy (Liu et al., 2003).

In a study from Los Angeles, CA, that focused on CO and PM, no results were reported from a single-pollutant model of ozone (mean 24-h average: ~20 ppb), but when four pollutants (NO₂, CO, O₃, PM₁₀) were modelled together, preterm birth was significantly associated with exposure to ozone in the first month (RR = 1.23 (95% CI 1.06–1.42) per 1 pphm (10 ppb) ozone), first trimester (data not reported) and second trimester (RR = 1.38 (95% CI 1.14–1.66) per 1 pphm (10 ppb) ozone). No effects were reported during the 6 weeks before birth. Effects in the first month of pregnancy were stronger when data were stratified by exposure levels (RR = 1.45 (95% CI 1.16–1.80) for ozone concentrations ≥1.42 to <2.97 pphm; RR = 1.74 (95% CI 1.31–2.32) for levels ≥2.97 pphm). Associations with CO were strongest near CO-only monitors, and PM₁₀ and PM_{2.5} were generally not associated with preterm birth (Wilhelm and Ritz, 2005).

In a study from Brisbane, Australia, ozone (mean daily max 8-h average: 26.7 ± 7.8 ppb) was associated with significant increases in preterm birth during the first trimester (OR = 1.26 (95% CI 1.10–1.45) per 7.1 ppb) and non-significant increases during the last 90 d before birth (OR = 1.06 (95% CI 0.89–1.26) per 4.5 ppb). There was some indication of an increasing trend across the months of the first trimester (OR = 1.13 (95% CI 1.01–1.25), OR = 1.13 (95% CI 1.02–1.27) and OR = 1.25 (95% CI 1.11–1.42) for the first, second and third months, respectively). PM was also associated with preterm birth in the first trimester, but when ozone and PM₁₀ were regressed together, no significant effect was observed with either pollutant, although both remained marginally increased (e.g. for ozone OR = 1.16 (95% CI 0.98–1.39)) (Hansen et al., 2006).

In an earlier study from California, annual ozone concentrations at the nearest monitoring station (IQR = 6 ppb) in Los Angeles County between 1994 and 1996 were not associated with preterm birth (OR = 0.99 (95% CI 0.91–1.09) per 1 pphm (10 ppb)). Significant associations were observed with annual average concentrations of CO, though not with PM₁₀, or NO₂). The focus of this study was not on individual pollutant effects, but on the relation of LBW and preterm birth with DWTB (Wilhelm and Ritz, 2003).

15.6.2.5 Other Birth Outcomes

Only one study of other endpoints was identified. In a case-control study, Gilboa et al. (2005) assessed the relationship between air pollutants (PM₁₀, O₃, NO₂, SO₂ and CO) and eight clinical diagnostic groups of isolated or multiple birth defects in seven Texas counties between 1997 and 2000. In addition to confounders considered in many birth outcome studies (e.g. maternal age, parity, season, race or ethnicity, parental education, and prenatal care) several other factors were considered, including alcohol consumption during pregnancy, attendant of delivery, gravidity, marital status, maternal illness, place of delivery, plurality, and tobacco use during pregnancy. In contrast to what was expected, declines in the risk for isolated ventricular septal defects were associated with exposure to ambient ozone during weeks 3–8 of pregnancy (p-value for trend across quartiles: 0.0034). There was also an apparent concentration–response relationship (albeit non-significant) across quartiles of average ambient ozone concentration during weeks 3–8 of pregnancy and isolated pulmonary artery and valve defects, which they considered to provide support for an earlier California study reviewed in the US EPA 2006 Ozone AQCD. Associations with other pollutants included (with PM₁₀) an increasing trend of atrial septal defects, associations with pulmonary artery atresia without ventricular septal defects, and a suggestive association with isolated cleft lip with or without cleft palate; (with CO)

tetralogy of Fallot and multiple conotruncal defects; and (with SO₂) isolated ventricular septal defects and all ventricular septal defects combined. Quartiles of ozone were <18, 18 to <25, 25 to <31 and ≥31 ppb.

15.6.3 Reproductive Studies

In one study of sperm quality, exposure to 14.3 ppb ozone (mean 24-h average: 21.68 ± 9.43 ppb) in Los Angeles, CA, between 1996 and 1998 was associated with decreased sperm concentration 0–9 d (-2.80%, p = 0.04), 10–14 d (-2.36%, p = 0.04) and 70–90 d (-2.61%, p = 0.10) prior to donation (48 sperm donors; 5,134 semen samples). In a four-pollutant model, these associations were slightly higher (-4.22%, p = 0.01; -2.92%, p = 0.05; and -3.90%, p = 0.05, respectively). No associations were observed between the other pollutants (PM₁₀, CO, NO₂) and sperm concentration in either single- or multi-pollutant models; nor was sperm motility related to any pollutant. The authors suggested that declining sperm densities are geography-dependent and that ozone may be a potential sperm toxicant, without an (as yet) defined mechanism of action, although the generation of reactive oxygen species was put forward as a potential mechanism (Sokol et al., 2006).

15.6.4 Summary and Considerations: Epidemiology Studies of Developmental and Reproductive Endpoints

Researchers have only recently begun to investigate the effects of air pollution on birth outcome and reproductive endpoints. Therefore, there are few data with which to draw conclusions at this time.

In the small number of available studies that investigated perinatal mortality, both older and within the review period, there was no credible evidence that ambient ozone was associated with intrauterine or infant mortality, even at relatively high concentrations. Instead, in these studies mortality was consistently increased in relation to other pollutants (one or more of NO₂, SO₂, CO, or PM), though none of these clearly predominated.

With respect to birth weight, the evidence that ozone may increase the risk for LBW and/or cause reductions in birth weight is somewhat stronger than was the case at the time of previous assessments, though it still remains inconclusive. In a number of earlier and more recent studies, ozone-related risk estimates were positive for LBW and/or there were reductions in mean birth weight with ozone, particularly in the third (and sometimes second) trimester, though these associations were not always statistically significant. The nature, direction and temporal specificity of these apparent effects are generally coherent with patterns in fetal growth, where weight gain occurs primarily in the third trimester. In addition, there was an apparent concentration–response relationship with ozone in a few of the studies. Interestingly, in the study in which ozone was most clearly associated with LBW, this association appeared to follow a dose–response pattern and was only significant at concentrations greater than 30 ppb. There is also some support for an effect of ambient ozone on birth weight in the consistent findings of ozone-related increases in risks for SGA or for IUGR, again most often in the second or third trimester, in the small number of reviewed studies that examined these endpoints. However, the risk for LBW or for reduced birth weight in the available studies was more often significantly related to other pollutants, most often SO₂ and CO (although these were sometimes associated with other windows of exposure, e.g. the first trimester). In addition, while associations with ozone were robust to adjustment for other pollutants in some studies, they were rendered non-significant in others, and indeed sometimes ozone was associated with changes in birth weight

in the opposite direction from the expectation. These findings highlight the difficulty inherent in discerning any effects of ozone on birth weight from those of co-occurring (and sometimes strongly correlated) pollutants.

Based on the earlier literature and that reviewed for this assessment, there is little evidence that ambient ozone is associated with preterm birth. In most studies, there was no significant association between ozone and increased risk of preterm birth. In those studies where the two were related, the time period for the association was not specific to any particular window of pregnancy (in one study, there were increased risks for both the first and last trimester, but not the middle). In another study, the association with ozone was reduced to non-significance by adjustment for PM. In several of the studies reviewed, preterm birth was more strongly related to other pollutants, most often CO.

Studies of other developmental and reproductive outcomes are limited to two studies in which there was no consistent increase in specific categories of birth defects associated with ambient ozone, and another in which sperm concentrations were reduced in relation to ambient ozone, but not to other air pollutants.

15.7 Epidemiology Studies of Genetics

A number of studies have investigated the effects of ozone on markers of DNA damage, as well as susceptibility to the effects of ozone among different genetic subpopulations.

15.7.1 Summary of Previous Assessments

At the time of the 1999 Ozone SAD there were no published studies of the effects of air pollution on genetic endpoints. The US EPA 2006 Ozone AQCD noted that genetic factors likely contribute to the substantial interindividual variability in susceptibility to the pulmonary effects of ozone. The results of several studies reviewed in that assessment suggested that genetic polymorphisms of inflammatory genes and antioxidant enzymes (e.g. GSTM1, NQO1, and TNF polymorphisms) may modulate ozone-related pulmonary and inflammatory effects. In one study, asthmatic children from Mexico City who were deficient in GSTM1, a common polymorphism of an important gene in protecting cells from reactive oxygen species, had more pronounced decrements in lung function, and this effect was reduced by supplementation with antioxidant vitamins. In a second study, the presence of at least one NQO1 Ser allele (NQO1 is a detoxifying enzyme induced in response to oxidative stress) in asthmatic children that were GSTM1 *null* was protective against ozone exposure. Polymorphism in TNF- α , a pro-inflammatory cytokine gene implicated in pulmonary injury and inflammation in animals, was related to the risk of ozone-induced lung function changes in asthmatics and individuals with rhinitis. However, the US EPA pointed out that, while these findings suggest an influence for these genetic markers on susceptibility to the effects of ozone, these markers and their relevance to population studies required further validation. It was also noted that the lack of correlation between lung function and airway inflammatory responses to ozone in controlled studies, combined with evidence of separate loci for ozone-induced airway inflammation and AHR in mice, suggested that these two responses are regulated independently.

With respect to markers of DNA damage, increases in 8-OHdG (a DNA adduct generated by oxidative stress) were observed after healthy subjects were exposed to ozone, but only in subjects genotyped NQO1 *wt* and GSTM1 *null*. DNA damage in blood leukocytes and nasal epithelial cells was also observed in Mexico City after exposure to high concentrations of ambient pollution, including ozone. The US EPA 2006 Ozone AQCD concluded that genetics may influence an individual's innate susceptibility to ozone and noted that studies of better design could help to inform polymorphism–susceptibility links.

15.7.2 Genetic Susceptibility

Studies of genetic endpoints or the influence of genetics on pollutant-related outcomes have typically been conducted in California and Mexico, areas with high concentrations of ozone. Several studies comparing the effects on subjects residing in areas with different concentrations of ozone were excluded from this assessment. This decision was made because of either a lack of ozone data or a lack of regression analyses of health outcomes linked to ozone concentrations. These studies provide insight into the effects of high levels of air pollution rather than ozone per se.

In a cross-sectional study, conducted as part of the CHS in Southern California, weaker associations between ozone and asthma or wheezing were observed in subjects carrying a TNF-308GG genotype compared with those carrying TNF-308GA or TNF-308AA genotypes.

The TNF gene is expressed in the airways, and polymorphisms may affect their role in inflammation and AHR. Communities were divided into low and high ozone groups to account for uncertainties in indoor levels and time-activity patterns; the protective effect of TNF-308GG was more pronounced in communities with low ambient ozone (<50 ppb annual average) than in those with high ozone (≥50 ppb). In subjects genotyped TNF-308GG and GSTM1 *null* or GSTP1 *Ile/Ile*, the effects of ozone on wheezing or asthma were even greater and remained significant after differences in SES and ethnicity were accounted for. Considered together with earlier results that linked TNF-308AA and TNF-308GG to decreases in lung function and increases in inflammation, the evidence from genetic susceptibility studies suggests that there may be different mechanisms of action for changes in lung function than for asthma and wheezing (Li et al., 2006).

15.7.3 Genotoxicity

In African-American asthmatic mothers and children 4–12 years old residing in inner-city Oakland, CA, regional and seasonal ozone (mean 8-h average ozone ranged from ~15 ppb to 30 ppb) were associated with increased frequency of micronuclei (a marker for mutation) in buccal cells and lymphocytes. While the number of cigarettes smoked per household per day was adjusted for, passive and active smoking could not be separated (Huen et al., 2006).

In a pilot study in Mexico City, the association between personal exposure to air pollution and DNA damage (measured by the Comet assay) was compared between groups of indoor workers (estimated median ozone exposure 5.1–19.5 ppb) and outdoor workers (street vendors, taxi drivers, bus drivers; estimated median ozone exposure 28.5–36.1 ppb) in two cities. Simple and multiple logistic regression results suggested that personal occupational exposure to ozone was associated with an increased risk of individuals having highly damaged cells (≥60% cells with longer tails); however, the models' parameters were not described (Tovalin et al., 2006).

In a cross-sectional study of 79 healthy subjects from Florence, Italy, lymphocyte DNA breaks were correlated with exposure to ozone 7 and 30 d prior to sampling. However, this association was weaker than the association with air temperature and was not significant when modelled with air temperature and solar radiation. No associations were observed between ozone and another marker of DNA damage, Fpg-sensitive sites. In addition, the descriptions of the univariate and multivariate linear regression models used were very limited, and ambient ozone concentrations were not presented (Giovannelli et al., 2006).

In another Italian study, differences in DNA damage in the nasal mucosa between subjects residing in two cities were investigated. DNA damage (measured by the Comet assay) and ozone concentrations were both about 70% greater in Florence (high pollution, daily average ozone $75.17 \pm 18.37 \mu\text{g}/\text{m}^3$ (~ 38 ppb)) than in Sassari (low pollution, daily average ozone $44.88 \pm 8.81 \mu\text{g}/\text{m}^3$ (~23 ppb)). DNA damage was significantly and positively related to both long-term (average over the preceding month) and short-term (preceding day) ozone levels, but not to concentrations of SO₂, NO_x, or PM₁₀. The association with ozone was observed only in non-smokers, perhaps because increased DNA damage observed in smokers masked any effect of ozone. DNA damage and ozone exposure correlated with histopathological inflammation of the upper respiratory tract. Increased DNA damage was also associated with the inability to maintain normal epithelial cell structure, due to impairment of cell-to-cell adhesion (Pacini et al., 2003).

In a nested case-control longitudinal study of mortality from COPD and emphysema in non- and ex-smoker cancer patients (in the EPIC project) it was observed that ambient levels of ozone (not reported) were correlated with leukocyte DNA adducts measured years before the onset of

cancer in non-smokers (Peluso et al., 2005). In the same study it was observed that DNA adducts may predict lung cancer in lifetime non-smokers. This was an atypical air pollution study, however, and it is unclear whether all potential confounders were accounted for.

15.7.4 Summary and Considerations: Epidemiology Studies of Genetics

There has been an increase in studies of the genetic effects of air pollution, though the number of studies remains small.

Both older studies and those reviewed in this assessment have shown that genetic polymorphisms for antioxidant enzymes and inflammatory genes (GSTM1, NQO1, and TNF polymorphisms have been investigated) may influence the susceptibility of subjects to a range of health effects, including ozone-related decrements in lung function, inflammatory changes, and wheezing or asthma. The available studies have been primarily conducted on asthmatic children, though polymorphisms in TNF- α also appeared to modulate changes in lung function changes in rhinitis in one study reviewed by the US EPA. In general, more susceptible genotypes are those that express less of some aspect of the antioxidant defence system, or that are more proinflammatory.

Ambient ozone has also been associated with genotoxicity, including increases in micronuclei frequency and DNA damage in somatic cells, both in the respiratory tract and in circulating leukocytes and lymphocytes. Studies have been conducted with both healthy and vulnerable populations. In one Italian study, DNA damage in the nasal mucosa was more pronounced in communities with higher ozone concentrations than in those with lower concentrations, and was not related to other air pollutants. In one earlier study, ozone was associated with increases in 8-OHdG, a marker for oxidative DNA damage, in healthy subjects, but only in those that were genotyped NQO1 *wt* and GSTM1 *null*. Hence, the US EPA 2006 Ozone AQCD conclusion that genetics may influence an individual's innate susceptibility extends to some genotoxic endpoints.

In addition to highlighting the potential for genotype to influence individual susceptibility to ozone, research in this area has also reaffirmed the central role of reactive oxygen species as the likely toxic moiety for a variety of ozone-induced health effects.

Although the research has identified potentially susceptible genetic subpopulations linked to polymorphisms of antioxidant enzymes and inflammatory genes, the number of studies and range of genetic markers that have been examined remain small, and these (and other) markers and their relevance to population studies still require further validation.

15.8 Chronic Exposure Epidemiology

15.8.1 Summary of Previous Assessments

At the time of the 1999 Ozone SAD evidence from cross-sectional and longitudinal studies suggested that lung function decrements and increased asthma cases were associated with chronic exposure to high levels of ozone. The US EPA 2006 Ozone AQCD noted that relatively few studies had examined the association between chronic exposure to ozone and morbidity or mortality. The US EPA concluded that the strongest evidence was for effects of extended exposures to ozone in the summer season on reduced lung function growth in children at higher ambient ozone levels, which was reported in several studies. There was more limited evidence for risk of asthma development, in the form of significant associations between chronic exposure to high ozone concentrations (and not other pollutants) and new onset asthma cases in two longitudinal studies, restricted to subgroups that may spend more time outside: i.e. male adults and children who played three or more sports. There was little evidence of ozone-related effects on other morbidity endpoints, including yearly lung function (largely negative in studies of strongest design) and respiratory symptoms (more strongly related to PM and/or certain other pollutants). Longitudinal studies of the effects of chronic ozone on mortality and cancer incidence reported inconsistent results for all-cause and cardiopulmonary mortality and for lung cancer incidence; in those studies that presented analyses for other pollutants, these outcomes were instead related to PM.

15.8.2 Mortality

In prospective cohort studies of the health effects of air pollution reviewed for this assessment, mortality was most strongly and consistently related to chronic exposure to fine PM (Section 14.8), but there is also some limited evidence that long-term exposure to ambient ozone may contribute to increased mortality. In a re-analysis of the ACS Cancer Prevention Study II cohort, of approximately 500,000 people from 151 US metropolitan areas, cardiopulmonary mortality between 1982 and 1989 was significantly related to long-term warm season ozone concentrations (average 30.44 ppb) (RR = 1.08 (95% CI 1.01–1.16), for the change in mean ozone between the most-polluted and the least-polluted city) after adjustment for smoking, education, occupational exposures, BMI, marital status, and alcohol consumption (Krewski et al., 2000, p. 174). All-cause mortality was non-significantly increased with warm season ozone (RR = 1.02 (95% CI 0.96–1.07)), whereas the risk estimates were significantly decreased for all-cause and cardiopulmonary mortality in relation to cold season ozone, and for lung cancer mortality in both seasons. No multi-pollutant analyses were conducted to further investigate the association with ozone, though the fact that the increase was for the warm season only suggests that it was specific to ozone. Findings were similar in a subsequent follow-up that extended the follow-up to 16 years and tripled the number of deaths, but in the latter study the increased risk of ozone-related increase in cardiopulmonary mortality, reported only in a figure, was similar in magnitude but not quite statistically significant (Pope et al., 2002).

15.8.3 Diabetes

Only two chronic effect studies of morbidity published in the review period were identified. Hathout et al. (2002) examined the association between ambient air pollution and the development of type I diabetes before and after 5 years of age in Southern California using a

case-control design (study dates not presented). The study included 61 children with diabetes and 39 age-matched healthy controls residing in the same area. The investigators compared pre-diagnosis exposure to air pollution among children with early-onset diabetes to those with later-onset diabetes, and compared birth-to-diagnosis air pollution exposure in children with diabetes to pollutant exposures of the control group. Two-tailed t-tests were used to compare early-onset vs. later-onset diabetes; logistic regression with the Wald statistic was used to measure the strength of association between air pollution and diabetes. Pre-diagnosis average ozone concentrations (estimated at the centroid of the ZIP code where the child resided) were higher for children with diabetes than for controls (mean ozone concentrations were 32.45 ppb and 26.64 ppb, respectively ($p = 0.031$) for children with onset ≤ 5 years of age, and 32.73 ppb and 27.12 ppb ($p = 0.007$) for children with onset after age 5), but ozone exposure did not differ significantly between cases that were diagnosed before 5 years of age and those diagnosed afterward. Ambient ozone was associated with type 1 diabetes for all ages combined in crude estimates (OR = 4.22 (95% CI 1.96–9.10) per 10.9-ppb ozone; the age-adjusted estimate was identical). The association was strongest for children >5 years of age (OR = 6.17, 95% CI 1.75–21.78) vs. children ≤ 5 years of age (OR = 3.25, 95% CI 1.22–8.67). However, the investigators noted that this may simply be due to greater cumulative exposure in older children. A similar or smaller increased risk of diabetes diagnosis for each of the two age classes was also associated with PM₁₀, whereas a decreased risk was associated with other pollutants (NO₂, SO₂ and SO₄). Multi-pollutant models were not assessed.

In an expansion of their earlier study, Hathout et al. (2006) analyzed data from 102 cases and 300 age-matched healthy controls. Chi-square tests were used for categorical data; t-tests and unconditional multivariate logistic regression were used to compare air pollution between cases and controls. Pre-diagnosis ambient average ozone concentrations estimated at the centroid of childrens' residential ZIP code were found to be higher among children with diabetes (mean 29.4 ppb) than among controls (25.8 ppb). Passive smoking, history of diabetes and autoimmunity in the family, and family drug abuse were also higher in children with diabetes than in controls, whereas daycare attendance, history of breastfeeding, and parental college degree were significantly lower in children with diabetes than in controls. Ozone exposure was associated with the odds of a child being diagnosed with type I diabetes (OR = 2.92 (95% CI 1.86–4.58) per 10-ppb ozone). This estimate was robust to the inclusion of potential confounders (e.g. ETS, daycare attendance, maternal diabetes, breastfeeding, family history of diabetes or autoimmunity, maternal drug use and highest parental education). The investigators suggested that ozone may be a predisposing or accelerating factor for the development of type I diabetes (i.e. by causing free-radical damage to β -cells or enhancing the presentation of diabetogenic antigens). They also noted that there may be a synergistic effect with SO₄ in ambient air. Type 1 diabetes diagnosis was also significantly associated with SO₄, but not with SO₂, NO₂ or PM₁₀. Multi-pollutant models were not assessed.

15.8.4 Summary and Considerations: Chronic Exposure Epidemiology

In previous assessments, it was concluded that longer-term exposure to ambient ozone was associated with lung function decrements and/or increased asthma cases. However, even for the ozone-related morbidity for which the findings are fairly consistent (associations of seasonal ozone with reduced lung function/lung function growth, and development of asthma), the number of studies is quite small, and for the lung function effects there are questions about the possible role of other pollutants in some studies. The chronic effects studies published in the review period are limited to two related studies suggesting that ozone may be associated with incident Type 1 diabetes in children; however, further evaluation is required to confirm these findings. With respect to other morbidity endpoints, there is little evidence from epidemiological

studies of effects of chronic exposure to ozone on lung function, or on respiratory symptoms or inflammation.

Though little information reviewed in this and earlier assessments indicated that chronic exposure to ozone was related to mortality, in an earlier report of the largest study, analysis of the ACS cohort indicated that long-term ambient ozone concentrations were marginally but significantly related to cardiopulmonary mortality; however, these findings require confirmation and additional analysis, including investigation of cause-specific mortality and adjustment for co-pollutants.

15.9 Risk Characterization

15.9.1 Introduction

Risk characterization serves an integrative function in an assessment. That is, the risk characterization seeks to integrate the scientific information provided on the nature and concentrations of the “hazard” to which receptors are exposed (in this case, the pollutant ground-level ozone), the nature of the effects induced by exposure to the hazard (ozone-related effects reported in epidemiological studies and in toxicological studies in humans and laboratory mammals), and the quantitative relationship(s) between exposure of receptors and the responses they exhibit (i.e. the concentration–response relationships). Together, this information is used to estimate the magnitude of impacts expected under current (and future) exposure conditions.

This section presents the first part of such an analysis. Summaries of the key information on exposure and effects of ozone described in detail in sections 15.1 to 15.8 are presented here. The summary information is then presented in an integrated fashion and the weight of evidence is evaluated to assess whether the findings support a causal association between exposure to ground-level ozone and various categories of health effects. The shape of the concentration–response curve and the populations that are most at risk from exposure to ozone by virtue of having enhanced exposure and/or susceptibility are also described. Uncertainties in the data and the implications of these uncertainties are discussed. Finally, conclusions with respect to key findings and insights from the preceding subsections of the risk characterization are presented.

Quantitative assessments of the relationships between ozone and adverse health effects can be developed and presented separately using Health Canada’s Air Quality Benefits Assessment Tool (AQBAT). These quantitative relationships are based on an analysis of the literature that provides the most appropriate results for this purpose, and utilizes the results of both single studies and meta-analyses of multiple studies. AQBAT has been and is used to estimate the benefits of air quality risk management in federal Regulatory Impact Assessments and in establishing the potential benefits in air risk management scenario development. AQBAT includes endpoints for which strong evidence of a relationship between exposure and effect has been established. This spreadsheet tool is available upon request to air@hc-sc.gc.ca.

15.9.2 Summary of Exposure and Effects

15.9.2.1 Summary of Exposure

The understanding of exposure, especially as represented by community air quality monitors, informs the interpretation of the epidemiological evidence. Much research has been conducted in this area, with recent efforts providing additional insights as to the relationship of personal and population exposure to ozone with the concentrations measured at central site monitors.

There are few indoor sources of ozone, but the entire population is exposed to ozone of ambient origin, especially when people are outside but also when they are in indoor environments into which ambient ozone has infiltrated. As described in Section 15.1.1, ambient ozone levels display marked variations in time and space. Concentrations of ground-level ozone vary throughout the day, and are greatest in either the afternoon or evening in different regions. Levels also fluctuate during the course of the week and are often greatest on weekends. Seasonal maxima are observed in the summer or spring, depending on the region. There are

also substantial geographical differences in ozone levels; concentrations are greatest in the southern parts of Ontario and Quebec, which are the principal regions where the current ambient standard for ozone is exceeded. As well, although concentrations of ozone at various locations within a region are often highly correlated because ozone is a secondary pollutant, this is not always the case, because levels still vary on smaller spatial scales: for example, levels are increased in rural areas downwind of major sources of precursor gases (e.g. urban centres), while they are most often reduced in the downtown core, near roadways, and indoors as a result of chemical reactions (Section 15.1.2).

As a consequence of these variations in ozone levels, personal exposures to ozone will vary over time and as an individual moves among locations. As presented in Section 15.1.3, a number of US and Canadian studies have investigated personal exposures to ozone, including the relationship between these exposures and the concentrations measured at central sites, which are used as a measurement of population exposure in most epidemiological studies. These studies have shown that personal exposures to ozone are typically less than the concentrations measured at ambient/other outdoor sites and greater than those indoors, and they revealed large differences in exposure between subjects. In spite of these variations, in virtually all of the available studies, measured personal exposure to ozone for groups or individuals was moderately to strongly related to concentrations at a central site, with correlation coefficients of around 0.4 to 0.6 or statistically significant regression slopes. Personal monitoring studies from Canada and the US also showed that mean personal exposures to ozone follow the same temporal trend as the concentrations measured at a central site. In most studies, personal exposure was related to time spent outdoors and/or was greater in summer, when ambient ozone levels, time spent outdoors, and building air exchange rates (and hence infiltration) are generally greater. In addition, increased ventilation (e.g. opening windows) often increased personal exposure to ozone in these studies.

These findings confirm the importance of ambient ozone to personal exposure and indicate that, although concentrations measured at a central site may not account for interindividual differences in exposure to ozone, they appear to be a reasonable surrogate for personal exposure at a population level. In addition, though personal exposures are generally somewhat less than the corresponding ambient levels, day-to-day variations in ozone exposure of the population are likely to track changes in the concentrations measured at central sites. It is these variations over time and the ability to represent population average personal exposure, rather than the absolute magnitude of the exposure itself, that are the basis for the associations between ambient ozone air pollution and the health effects reported in the time-series epidemiology studies. Therefore, ambient concentrations are a useful and appropriate exposure measure for epidemiologic studies.

The relationship between ambient concentrations and personal exposure to ozone will vary as a result of individual-, city-, or region-specific differences, resulting in measurement error and potential bias in risk estimates. The bias can be either upward or downward, but is expected to most often underestimate risks and to make it more difficult to detect a health effect under a “classical” measurement error model. However, exposure measurement error also makes detecting the true shape of the exposure–response association more difficult.

Outdoor workers, children and exercising individuals are known to have increased exposures to ambient ozone, because they generally spend more time outdoors and are active, often during the season and time of day when concentrations of ozone are greatest (Section 15.1.3). It is also known from toxicology studies in animals (Section 15.3) and in humans (Section 15.4) that prolonged exposure to ozone in combination with exertion (features that characterize the above groups) can increase exposure and enhance the respiratory effects of ozone. Consequently,

outdoor workers and others who are active outdoors when peak ozone concentrations occur should be considered a vulnerable subset of the population.

15.9.2.2 Summary of Effects in Laboratory Animals

Compared with PM there is less ongoing ozone toxicology research, though owing to its physicochemical simplicity the progression of lung injury and mechanisms of action have been relatively well characterized. As detailed in Section 15.3.1.1, acute ozone exposure damages epithelial airway tissue, increases airway permeability, and causes lung inflammation mediated by AM activation, neutrophil influx and increased levels of inflammatory cytokines and reactive oxygen species. These effects have been observed in rodents with ozone exposure levels as low as 0.1 ppm. Ozone reacts with substrates in the epithelial lining fluid of the lung, depleting protective antioxidants such as ascorbic acid and glutathione while damaging proteins and oxidizing lipids. Long-term ozone exposure has been observed to cause morphological changes in the respiratory tract of laboratory animals, including airway remodelling in the centracinar region and nasal hyperplasia and mucous cell metaplasia in the upper respiratory tract.

It has been established that acute ozone exposure can alter breathing patterns and cause rapid shallow breathing in rodents. This response appears to produce a more evenly distributed injury pattern rather than protection from damage. Work with inbred mouse strains suggests that the control of ventilatory responses to ozone is determined, at least in part, by genetic factors. Concomitant with a heightening interest in asthma and allergic responses to air pollution, studies on pulmonary function have increasingly moved towards measures of airway sensitivity (Section 15.3.1.2). Ozone is thought to exacerbate airway reactivity to specific allergens in asthmatics by nonspecifically increasing AHR. Acute exposures to ozone in the range of 0.5–1 ppm have been shown to heighten AHR in laboratory animals, a response that persists longer and attenuates more slowly than pulmonary function decrements or respiratory symptom responses. Ozone may induce AHR by modulating rapidly adapting airway receptors or by altering the structure of conducting airways; the release of neuropeptides such as substance P from intrinsic airway neurons may also play an important role. The link between AHR and inflammation is not entirely clear, as some evidence points to the involvement of inflammatory mediators in this response (e.g. induction of IL-1 β , complement activation), but the database is not entirely consistent. A synergistic interaction between acute ozone exposure and allergens such as ovalbumin in evoking inflammatory and pulmonary function responses (such as increased airway resistance and elevated immune markers) has been demonstrated in a number of experimental allergy models using sensitized rats, mice and guinea pigs (Section 15.3.1.3). These studies provide mechanistic support to reports of ozone-induced exacerbation of AHR in atopic humans with asthma.

Ozone may indirectly affect organs beyond the respiratory system through the transport of reaction products in the bloodstream to target sites, or via exposure-related production of inflammatory and metabolic mediators. An increasing amount of toxicological research concerns the systemic effects of ozone beyond the lungs. As presented in Section 15.3.3.1, a body of evidence now suggests that inhalation of ozone at exposure levels as low as 0.2 ppm may lead to adverse effects in the CNS of laboratory animals. A range of neurological effects have been reported, such as altered brain catecholamine levels, dopaminergic neuron dysfunction, morphological changes such as reduced neuron density, and lipid peroxidation in brain tissue. Associated behavioural effects include short- and long-term memory deficits, altered EEG patterns during sleep, and decreased motor activity and exploratory behaviour. Many of these CNS responses are accompanied by evidence of oxidative stress, and their alleviation or prevention by antioxidant administration supports a role for this mechanism. Overall, however, information on the biochemical and molecular mechanisms behind these effects remains rudimentary.

Ozone has been linked to effects on the cardiovascular system but the evidence base is less developed than that for PM. Effects reported in rodents from exposure to ozone in the range of 0.1–0.5 ppm include reduction in heart rate, arterial blood pressure and core temperature, and increased frequency of arrhythmias (Section 15.3.3.2). Direct ozone effects such as the release of platelet activating factor from lung epithelial cells could potentially contribute to blood clot formation, increasing the risk of serious cardiovascular outcomes. It has also been recognized that the interaction of ozone with surfactant components in the lung epithelial lining fluid may result in the production of oxysterols and reactive oxygen species that may exert cytotoxic effects on lung and heart cells and/or contribute to clotting. Indirect effects such as the stimulation of vasoconstrictor secretion and effects on neuronal reflexes have been hypothesized to lead to increased arterial blood pressure and altered electrophysiologic control of heart rate or rhythm.

Experimental animal studies have investigated numerous factors that may augment susceptibility to ozone, including physiological, age-related and genetic parameters (Section 15.3.4). Susceptibility to ozone appears to be, in part, genetically determined, as suggested by studies in which assorted strains of mice and rats were found to differ with respect to their vulnerability to ozone-induced lung injury and inflammation. Genetic and molecular characterization studies have identified chromosomal loci that were at least partly responsible for both the sensitivity and resistance of laboratory animals. There is some evidence that immature and aged rats are more sensitive to ozone than adult rats. Also, several studies have reported that obesity produces greater innate and ozone-induced airway reactivity responses, which may be explained by the higher levels of systemic inflammation observed in several strains of obese vs. normal mice. Short-term ozone exposure can increase susceptibility to infectious diseases due to the modulation of host defences in the lung (Section 15.3.2). Exposure of laboratory animals to ozone has been found to disrupt AM function and reduce lung clearance, decrease the T- and B-lymphocyte population, and impair antiviral responses, all of which can ultimately lead to increased mortality and morbidity from the weakened resistance to infectious microorganisms.

There are interesting findings concerning the effects of ozone on postnatal lung development in infant rhesus monkeys. As described in Section 15.3.5, subchronic episodic exposure of these animals to 0.5 ppm ozone was found to produce remodelling of the distal lung characterized by reduced branching of the conducting airways, abnormalities in the tracheal basement membrane, and decrements in airway innervation. These data suggest that ozone at high enough concentrations could compromise the postnatal morphogenesis of tracheobronchial airways. Studies of the developmental effects of prenatal ozone exposure generally show that concentrations below 1 ppm do not cause major or widespread somatic or neurobehavioural effects in the offspring of laboratory animals. Gestational exposure to 1 ppm ozone has been linked to cellular changes in the cerebellum of male rat offspring, while altered behaviour was reported in the adult offspring of mice exposed during gestation to ozone levels as low as 0.3 ppm. There is recent evidence in male rats of an adverse effect of subchronic exposure to 0.5 ppm ozone on germ cells and histopathological changes in the testes, possibly linked to oxidative stress.

Studies of ozone carcinogenicity and genotoxicity remain limited, as shown in Section 15.3.6. Genotoxic effects of ozone have been reported *in vivo*, including increased DNA strand breaks and cellular mutation frequency, but only with relatively high exposure levels. The results of *in vitro* studies in which genotoxicity was reduced by pre-treatment of cells with antioxidants suggest a role for oxidative damage. Regarding carcinogenicity, the weight of evidence does not appear to support ambient ozone as a pulmonary carcinogen in experimental animals. Lifetime

and 2-year inhalation studies of ozone carcinogenicity were negative in rats, while studies with mice reported equivocal results.

In the area of mixture toxicology there is some evidence for interactive effects in laboratory animals following combined exposure to ozone and other pollutants, but research in this area is limited and inconclusive (Section 15.3.7). Most interactions that have been observed with other substances like PM and NO₂ occurred only at higher than ambient concentrations.

15.9.2.3 Summary of Effects in Controlled Human Exposure Studies

In controlled studies of humans reviewed in this report and in previous assessments, inhalation of ambient or slightly greater concentrations of ozone caused a variety of effects, almost exclusively on the respiratory system (Section 15.4). Effects observed were most often reduced lung function (decreased FVC and/or FEV₁), and symptoms of breathing discomfort, but also included decreased inspiratory capacity, mild bronchoconstriction, shallow rapid breathing during exercise, as well as increases in AHR, inflammation, activation of the immune system, and epithelial injury. Spirometric and symptom responses to ozone are observed at lower concentrations during exercise, so most studies exposed subjects while engaged in physical activity.

In a number of earlier and more recent studies, healthy adults exposed to 0.08 ppm or more of ozone for periods of 4–8 h with exercise had significantly reduced lung function, manifested as transient decrements in FEV₁, along with increased respiratory symptoms (sections 15.4.1 and 15.4.2). Ozone-induced decrements in FEV₁ in healthy young adults were affected by the pattern of exposure: triangular exposure profiles (mimicking the daytime variation in ozone) gave rise to greater responses than did square wave exposures of equivalent average concentrations. Respiratory effects were also related to age, with similar spirometric responses and fewer symptoms in children than in young adults; both effects declined with age, beginning in early adulthood. In addition, substantial intersubject variability was noted even at the lowest effective concentration, although responses tended to be reproducible for a given individual over a period of several months. However, effects on spirometry and symptoms were not related to a range of other factors, including gender, race, body surface area, height, lung size, or baseline FVC.

Inflammation in the lung and respiratory tract was also reported in some studies, most often as an increased influx of neutrophils in the respiratory fluids and/or epithelium, though soluble mediators of inflammation, including cytokines and arachidonic acid metabolites, were also detected in the BAL fluid of humans exposed to ozone (sections 15.4.1 and 15.4.3). The bronchoconstrictive properties of a number of these compounds suggest that they may be involved in increased airway responsiveness following ozone exposure. The results of a limited number of studies suggested that inflammatory responses occurred at concentrations that did not affect lung function, and the two types of effects were not strongly correlated.

With repeated exposure to ozone over several days, effects were attenuated over time (sections 15.4.1, 15.4.2.2, and 15.4.3.2). This was most pronounced for spirometric and symptomatic responses, and less so for AHR. While some inflammatory markers (e.g. PMN influx, IL-6, PGE₂, fibronectin) showed attenuation, other markers of inflammation or lung injury did not (LDH, IL-8, total protein, epithelial cells), suggesting ongoing tissue damage with repeated exposure to ozone. Hence, attenuation of clinical effects is not necessarily an indication of attenuation of overall toxicity, and effects that are arguably more serious may continue on in the absence of clinical effects.

With respect to populations that may be susceptible by virtue of having pre-existing disease, asthmatics and allergic rhinitics had similar or slightly increased ozone-induced spirometric

responses, and increased inflammatory responses (in asthmatics) compared with healthy young adults. With repeated exposure to ozone, attenuation of spirometry was observed in asthmatic subjects, but AHR increased in subjects with allergic airway disease (with or without asthma) (Section 15.4.1). Since asthmatic patients have lower baseline values for most spirometric parameters than healthy subjects, a further decrease in FEV₁ caused by ozone could potentially take it below the threshold associated with asthma attacks. Acute exposure to ozone has also been shown to enhance AHR in asthmatics in combination with common allergens (Section 15.4.1). AHR is a hallmark of asthma, and collectively these results provide a possible explanation for the associations of ozone with increased risks for hospitalizations and ERVs for respiratory causes. There was little evidence of pulmonary or cardiovascular effects in subjects with COPD or CVD, possibly due to the greater age of subjects with these conditions (Section 15.4.1).

On another front, the results of some studies indicated that genetic polymorphisms for certain antioxidant enzymes and inflammatory genes (GSTM1, NQO1, and TNF- α) modulate ozone-related lung function, inflammatory responses, and oxidative stress, which may confer susceptibility on some subjects (Section 15.4.1).

In controlled human exposure studies, dietary supplementation with antioxidants provided some protection against the effects of ozone on spirometry and on biomarkers of oxidative stress, but not against the intensity of symptoms or pulmonary inflammation, injury or permeability. Dietary antioxidants also partially attenuated ozone-induced bronchial hyperresponsiveness in asthmatics (Section 15.4.1). These findings suggest that the various categories of ozone-induced effects are independent of one another, as well as highlighting the important role for ROS in the toxicity of ozone.

Controlled human exposure studies continue to provide only weak evidence to support the hypothesis that exposures to mixtures of pollutants have greater effects than single-pollutant exposures, though some early studies indicated that prior exposure to ozone enhanced SO₂-induced bronchial hyperreactivity, as well as spirometric responses to NO₂ and sulphuric acid (Section 15.4.1).

In the study in which exposure–response at low concentrations was best characterized (Section 15.4.2.2), there were apparent concentration-related decrements in lung function and increases in respiratory symptoms in healthy adults at all concentrations tested, including the lowest (0.04 ppm). Considering the apparent dose-related effects down to the lowest concentrations tested, the limited statistical power in all studies, and the large variation in susceptibility to ozone observed among the subjects in these studies, it is not possible to identify a concentration that is without effect based on the available controlled human exposure studies (Section 15.4.5).

15.9.2.4 Summary of Effects in Epidemiological Studies

15.9.2.4.1 Acute mortality

Large numbers of observational epidemiology studies, including single-city, multi-city and meta-analyses, have shown that short-term ambient ozone concentrations are associated with an increased risk of total non-accidental mortality (Section 15.5.1; Figure 15.5; Figures 7-14 and 7-15 in the US EPA 2006 Ozone AQCD). In the studies reviewed in this Assessment and in earlier assessments, the risk estimates for total mortality in relation to ozone concentrations over periods of a day or less were virtually all positive, and many were statistically significant after adjustment for potential confounders such as time and weather, particularly in those studies of strongest design. These associations were observed in cities from all regions of the world, including North and South America, Europe, Australia and Asia, in spite of large differences in climatic conditions, pollutant mixtures, and socioeconomic factors. The risk estimates were also

fairly robust to model specifications, including adjustment for PM and other co-occurring pollutants, and were consistently greater during the warm season than during the cool season or in all-year analyses; both of these findings indicate that this mortality is specific to ozone, which is the only common air contaminant that is predominantly a summertime pollutant.

A number of important features of the evidence for mortality related to ozone are illustrated by analyses of the NMMAPS, a large database of mortality from almost 100 US cities with many years of follow-up, and consequently great statistical power. In a NMMAPS report of particularly strong design reviewed in this Assessment, total non-accidental mortality was associated with ambient ozone, using 14 years of data from 98 US cities (Section 15.5.1.2). Using a log-linear model, the study found that the overall risk of dying increased 0.21% (95% PI 0.11–0.31%) at lag 0–1 d for every 6.7 ppb ozone 24-h average, and increased 0.19% (95% PI 0.07–0.30%) for the same increment when restricted to those days with a maximum 8-h ozone ≤ 65 ppb (the numerical value of the CWS for ozone). The shape of the concentration–response curve was extensively analyzed using several approaches, and the results indicated that total mortality was related to ambient ozone down to very low concentrations (i.e. it was quasi-linear at concentrations greater than 10 ppb 24-h average), providing little or no evidence of a threshold level below which effects were not observed. (This concentration is routinely exceeded at monitoring stations across Canada.) In addition, while the largest risk estimate was observed with a 0-d lag, increased risk was spread over several days following acute ozone exposure, and the risk estimate for the cumulative effect from the same day and six previous days was more than twice as large as the same-day estimate. Along with similar findings reported in some other studies, these results indicate that ozone-related effects may persist over longer periods and be associated with higher cumulative risks than single-day estimates would suggest. Finally, earlier analyses of the NMMAPS dataset revealed significant heterogeneity in the effect estimates from the individual communities, which was partially attributed to differences in pollutant mixtures, use of air conditioning, time-activity patterns, and socioeconomic factors. These findings suggest that the heterogeneity that exists in the larger literature has a real component, and is not solely or primarily the result of differences in model specifications among studies (in fact, as noted above, findings in these studies are generally not highly sensitive to the modelling employed).

Relatively few studies have examined more specific causes of death or susceptible subpopulations, and these have often had limited statistical power (Section 15.5.1). Nonetheless, the risk estimates for cardiovascular mortality in the epidemiological studies reviewed in this Assessment and in earlier assessments were virtually all positive, and many were statistically significant, though some heterogeneity across studies is evident (Section 15.5.1, Figure 15.7). For respiratory mortality, risk estimates were less consistent than for deaths from all-cause or cardiovascular causes in the studies reviewed in earlier assessments, though they were often positive and statistically significant in the studies reviewed in this Assessment (Section 15.5.1, Figure 15.6). There was no clear consistency in ozone-related mortality from more specific causes in the studies reviewed, and questions still remain with respect to the role of other pollutants in the observed associations. The evidence that ozone-related mortality is greater in potentially susceptible subpopulations is limited, though there is some suggestion in the few available studies of increased risks in people with severe asthma or COPD, and in the elderly (Section 15.5.1).

15.9.2.4.2 Hospital admissions

In studies of hospital admissions reviewed in previous assessments and in this Assessment, ozone was generally found to be positively associated with hospitalizations for respiratory conditions (most often total respiratory, COPD or asthma) during the warm season in a number of studies from the US and Canada, Europe, Asia and Australia (Section 15.5.2). In most cases,

these effects were observed at levels of ozone commonly encountered in Canada, were greatest with little or no lag, and were robust to adjustment for co-occurring pollutants, most often PM. In addition, asthmatics and older adults were identified as being potentially more susceptible, though risk estimates were positive for most age categories. The results of two of the stronger recent multi-city studies from the US and Australia provide support for these conclusions, with ambient ozone being related to admissions of older adults for each of COPD, asthma, or pneumonia. The 1999 Ozone SAD reported that respiratory hospitalizations were increased by approximately 1% per 10 ppb daily 1-h max ozone in a number of meta-analyses and multi-city studies. The results of more recent studies are generally not far removed from this estimate, though greater risks were observed over longer time periods (e.g., increases of several percent related to ozone averaged over several days) in some studies. Investigations of the shape of the concentration–response relationship in the 1999 Ozone SAD revealed that respiratory admissions increased in an ozone concentration-dependent fashion, without showing an obvious threshold at levels as low as 20 ppb daily 1-h max ozone. A number of other studies, though not all, summarized in the US EPA assessment also reported a similar monotonic increase in respiratory hospitalizations throughout the range of ambient ozone concentrations.

The association between ozone and cardiovascular admissions has been less studied and is less consistent than for respiratory hospitalizations. The US EPA assessment noted that cardiovascular admissions demonstrated increased associations in only some of the limited number of studies available at that time. Most of these positive studies examined ozone levels that were relatively high, and during the warm season. The results of the small number of more recent studies reviewed in this Assessment were generally similar. In two recent European studies, positive associations were observed between warm-season ozone at relatively high concentrations and hospitalizations for cardiovascular outcomes as a whole or for more specific conditions (angina pectoris, heart disease); these associations were stable in models that included other pollutants. In other studies, some with relatively low ozone concentrations, there was no clear association of ambient ozone with cardiovascular admissions.

15.9.2.4.3 Emergency room visits

The results of studies of ERVs generally confirm the respiratory effects reported in the hospital admissions studies. In a number of ERV studies reviewed in previous assessments and in this Assessment, there was a consistent positive association between ambient ozone and increased ERVs for asthma, when contemporaneous variables such as weather (particularly temperature) and co-pollutants had been properly controlled for. These associations were found in studies from Canada as well as other parts of the world, including the US, Europe, and South America. Excess risks were greatest with short lag periods (0 to 2 d), and were reported primarily in the warm season. Among the studies that reported a positive association between ambient ozone and ERVs for respiratory outcomes, ozone effects were generally found to be robust to adjustment for other pollutants or were not related to other pollutants. Increases in total respiratory ERVs were more pronounced in adults and seniors, whereas those for asthma visits were most often observed in children and sometimes in working-age adults. In studies reviewed in the 1999 Ozone SAD, asthma ERVs were increased by 6–8.6% per 10 ppb increase in 1-h max ozone, and the mean summertime ozone levels (1–5 h metrics) varied between 30 and 90 ppb. The risks reported in more recent studies are generally not far removed from these estimates.

The data reviewed on other medical visits and related endpoints are too limited to draw any firm conclusions. In single studies of cardiovascular endpoints, ambient ozone was not significantly related to ERVs for stroke or for ischemic cardiac disease, both of which were instead

associated with other pollutants. Ambient ozone was related to increases in school absenteeism in a small number of studies reviewed in this and earlier assessments.

15.9.2.4.4 Panel studies

The results from a large number of panel studies consistently indicate that acute ambient ozone exposure is associated with a significant effect on lung function, seen as decrements in FEV₁, FVC, and PEF, particularly in children, asthmatics, and adults engaged in outdoor physical activity (sections 15.5.4.1 and 15.5.4.2). These decrements were robust to adjustment for co-pollutants, most often PM. Use of antioxidant supplements was found to diminish the effect on lung function. There is little confirmation of these findings in the more recent literature, in which these susceptible groups were not studied or exposure levels were relatively low. A range of respiratory symptoms have been investigated in a number of studies, including several of the more recent ones reviewed, and overall the results indicate that short-term exposure to ambient ozone is related to increased asthma symptoms and increased as-needed medication use in asthmatic children, with no consistent results in healthy children. In some, though not all, of these studies the increase in ozone-related symptoms was robust to adjustment for other pollutants (sections 15.5.4.1 and 15.5.4.2). There is increasing evidence of a genetic basis to the susceptibility of certain individuals to ozone; genetic subpopulations with polymorphisms of antioxidant enzymes and inflammatory genes that confer differences in sensitivity to ozone-induced effects continue to be identified (e.g. susceptible individuals include GSTM1 *null*, HFE wild-type, and other genotypes) (sections 15.5.4.1, 15.5.4.2 and 15.7). With respect to biomarkers, ambient ozone has been associated with increased inflammatory markers and the generation of hydroxyl radicals in the upper airways, and in one more recent study with increased plasma levels of CRP and IL-6, markers of systemic inflammation, in older adults with diabetes, obesity and hypertension (sections 15.5.4.1 and 15.5.4.3).

Cardiac physiologic endpoints have been examined in a number of panel studies of older subjects (sections 15.5.4.1 and 15.5.4.4). While the current evidence, including the results of several more recent US studies, suggests an association between short-term exposure to ozone and HRV, cardiac arrhythmias, and MI incidence, the database remains fairly small, and associations with ozone were sometimes not statistically significant and/or the endpoints were sometimes more strongly related to other pollutants.

A range of effects have been associated with mean/median ambient ozone concentrations of less than 30 ppb for periods of between 1 and 24 h in some studies; these are levels commonly observed in Canada. Effects reported in such studies reviewed in this and earlier assessments include reduced PEF in healthy children, increased asthma symptoms in asthmatic children, as well as increased intermittent atrial fibrillations and decreased HRV in older adults.

A number of earlier and more recent studies have examined ozone-related effects in subgroups with pre-existing disease, including subjects with asthma, diabetes, obesity, hypertension, IHD, or COPD. The sensitivity of asthmatics to exposure to ozone has been well documented in previous assessments. For other disease groups indications do exist that ozone's inflammation-generating properties could be of importance. However, the limited number of identified panel studies and the null findings reported in some studies preclude drawing any conclusions with respect to the sensitivity of other subgroups from these studies at this time.

15.9.2.4.5 Effects of chronic exposure

Relatively few epidemiology studies have examined the health effects of longer-term exposure to ambient ozone. The evidence is strongest for seasonal effects of ambient ozone on lung function growth in children (Section 15.8.1). This was observed in several studies as reduced rates of growth-related increases in FEV₁ and/or FVC associated with summertime exposure to

relatively high ambient ozone levels. There was also more limited evidence for risk of asthma development, in the form of significant associations between chronic exposure to high concentrations of ozone and new onset asthma cases in longitudinal studies, restricted to subgroups that may spend more time outdoors (male adults, or children who played three or more sports). Studies investigating a variety of other health outcomes, including lung function on a yearly basis, respiratory symptoms, inflammation and the incidence of cancer, have yielded little evidence of an association with chronic exposure to ozone. The more recent chronic effects literature reviewed is limited to two related case-control studies from Southern California, the results of which suggested that ozone may be associated with incident Type 1 diabetes in children; there was little indication of a role for other co-occurring pollutants (Section 15.8.3). It should be noted that the number of available studies is quite small even for the ozone-related morbidity for which the findings are somewhat consistent, and there are questions about the possible role of other pollutants in some of the observed associations. Additionally, the 2000 re-analysis of the ACS cohort, while not indicating an effect of ozone in the main analysis, did find a positive and significant effect of summer ozone on cardiopulmonary mortality, indicating at least a potential effect of some importance (Section 15.8.2).

15.9.2.4.6 Developmental and reproductive effects

There is growing, though still inconclusive, evidence that ambient ozone may increase the risk for LBW and/or cause reductions in birth weight. In a number of earlier and more recent studies, ozone-related risk estimates were positive for LBW and/or there were reductions in mean birth weight with ozone, particularly in the third (and sometimes second) trimester, though these associations were not always statistically significant (sections 15.6.1 and 15.6.2.2). The nature, direction and temporal specificity of these apparent effects are generally coherent with patterns in fetal growth, where weight gain occurs primarily in the third trimester. In addition, there was an apparent concentration–response relationship with ozone in a few of the studies. There is also some support for an effect of ambient ozone on birth weight in the fairly consistent findings of ozone-related increases in risks for SGA or for IUGR, again most often in the second or third trimester, in the small number of reviewed studies that examined these endpoints (sections 15.6.1 and 15.6.2.3). However, the risk for LBW or for reduced birth weight in the available studies was more often significantly related to other pollutants (though these were sometimes associated with other windows of exposure, e.g. the first trimester). In addition, associations with ozone were not always robust to adjustment for other pollutants, and sometimes ozone was associated with changes in birth weight in the opposite direction from expectation (Section 15.6.2.2).

A small number of available studies, including those in earlier assessments and reviewed in this Assessment, investigated other birth outcomes. In the available studies, there was no credible evidence that ambient ozone was associated with intrauterine or infant mortality, even at relatively high concentrations (sections 15.6.1 and 15.6.2.1). Instead, mortality was consistently increased in relation to other pollutants, though none of these clearly predominated. Similarly, there was little evidence that ambient ozone was associated with preterm birth (sections 15.6.1 and 15.6.2.4); associations with ozone were either not significant, not specific to any particular period of pregnancy, or were not robust to adjustment for other pollutants. In several of the studies reviewed, preterm birth was more strongly related to other pollutants, most often CO.

15.9.3 Weight of Evidence for Various Categories of Effects

15.9.3.1 Introduction and Criteria for Causality

The experimental studies in humans provide compelling evidence that exposure to ozone causes various respiratory health effects, and indeed the findings in these studies were in large measure the basis for early regulatory controls to limit the formation of ground-level ozone. However, for ethical and practical reasons the controlled human exposure studies are generally limited to examining short-term, mild, reversible alterations in health endpoints, typically in small groups of relatively healthy individuals who do not include those who are most at risk (e.g. those with severe pre-existing disease). They are therefore unable to capture the full range of severities of effects and the profile of affected populations, and do not have the statistical power to identify relatively small risks.

The epidemiology studies can provide highly relevant and somewhat complementary evidence of the adverse health effects of ozone air pollution, inasmuch as they investigate responses in the general population (including susceptible subgroups) to exposure to ground-level ozone as a component of the ambient mix of pollutants in “real world” settings. They can also often examine more serious health outcomes and/or very large numbers of people. However, these studies are observational rather than experimental, and the information on both exposure and effects is generally only available for the population rather than individuals. As a consequence of such limitations, there is uncertainty as to whether the effects reported in the epidemiology studies are in fact due to ambient ozone alone, or if ozone is a marker, in whole or in part, for other toxic air pollutants.

To evaluate the weight of evidence that the epidemiological associations between health outcomes and ambient ozone are causal, it is necessary to examine the various lines of evidence in combination and to assess the collective evidence using established criteria for causal determination. In this section, the evidence for various categories of health outcomes is reiterated in an integrated fashion, by reporting the findings from the available controlled human exposure, animal toxicology and/or epidemiological studies together. This collective evidence is then evaluated for various categories of health outcomes in light of considerations that have traditionally been used to form judgments as to how likely it is that the observed associations are causal.

These considerations include

- the *strength of the associations*, including the magnitude and precision of the risk estimates and their statistical significance;
- the *robustness* of the associations to model specifications and adjustment for potential confounders such as weather, temporal trends, and co-occurring pollutants;
- the *consistency* of reported associations across studies and study designs conducted by different researchers in different locations and times;
- the *biological plausibility* of the associations in light of what is known regarding ozone dosimetry and the types of effects observed and associated potential mechanisms of action, based largely on animal toxicology and controlled human exposure studies; and
- the *coherence* of the relationship between exposure to ozone and related endpoints within and across animal toxicology, controlled human exposure, and various types of epidemiological studies.

The above considerations are then used to conclude whether the association with a given health effect or related set of health effects is causal, likely to be causal, suggestive of a causal relationship, or inadequate to conclude that the relationship is causal.

The evidence that specific subgroups of the general population are more at risk to the health effects of ozone, by virtue of increased exposure and/or susceptibility, is also considered in this section, and the shape of the concentration–response relationship between ozone and health effects is discussed in Section 15.9.4. These both have implications for the weight of evidence and the public health significance of the effects that are associated with ambient ozone.

15.9.3.2 Respiratory Morbidity Associated with Acute Exposure

15.9.3.2.1 Lung function

The strongest evidence for effects on lung function comes from a number of controlled human exposure studies, in which exercising healthy adults had significant decrements in lung function, most often FEV₁, following exposure to ambient or slightly greater concentrations of ozone for periods of several hours. In these studies, repeated measurements of the same individuals were highly reproducible, but there was large variability in pulmonary function responses between individuals, with some individuals being hyper-responsive to ozone. These findings were strongly supported by experiments in animals in which acute ozone exposure altered breathing patterns and caused rapid shallow breathing in rodents. In addition, the finding from studies of inbred mouse strains that resistance or susceptibility to ozone-induced effects on breathing was determined, at least in part, by genetic factors, provided plausibility to the large intersubject variability observed in the experimental human studies. In a large number of epidemiology studies, ozone-related decrements in lung function were consistently reported, particularly in subgroups that would be expected to have elevated exposure to ozone by virtue of being active outdoors (i.e. children, and adults engaged in physical activity outdoors) or to be susceptible because of pre-existing disease (i.e. asthmatics). These associations were robust to adjustment for co-pollutants, most often PM. Additionally, antioxidant supplementation, which would be expected to block certain adverse mechanisms, diminished the magnitude of the association with ozone.

15.9.3.2.2 Respiratory symptoms

Similar to lung function, the results of controlled human exposure studies provide the strongest evidence for effects of ozone on respiratory symptoms. In these studies, healthy adults inhaling ambient or near-ambient levels of ozone for periods of several hours while exercising consistently reported symptoms of breathing discomfort, such as cough, pain on deep inspiration, and shortness of breath. These symptoms were most pronounced in young adults, and less so in children or older adults, and like effects on lung function in these studies were attenuated with repeated exposure, suggesting that individuals can adapt to some degree. A range of respiratory symptoms have been investigated in panels of subjects in a number of epidemiological studies, and the results provide support for the findings in the controlled human exposure studies. Overall, in the panel studies acute exposure to ambient ozone was related to increases in asthma symptoms (e.g. cough, wheeze, production of phlegm, shortness of breath) and as-needed medication use in asthmatic children. In many of the panel studies, especially the larger ones, these increases in ozone-related respiratory symptoms were robust to adjustment for other pollutants.

15.9.3.2.3 Lung injury and inflammation

In controlled human exposure studies, exposure to ozone caused inflammation in the lung and respiratory tract, reported most often as an increased influx of neutrophils in the respiratory fluids or epithelium, and sometimes as increases in soluble mediators of inflammation; i.e.

cytokines and arachidonic acid metabolites. The results of some studies suggested that inflammation occurred at concentrations that did not affect lung function, and that the two were not strongly correlated. Some inflammatory markers showed attenuation with repeated exposure, whereas biomarkers of injury and some inflammatory markers did not, suggesting continuing toxicity with repeated exposure. In a limited number of epidemiology studies, there were ozone-related increases in inflammatory markers and the generation of hydroxyl radicals in the upper airways in children exposed to high ambient levels. In animals, the progression of lung injury and mechanisms of action have been relatively well characterized. Acute ozone exposure in these studies damages epithelial tissues and increases permeability in the airways, and causes lung inflammation characterized by AM activation, neutrophil influx, and increases in inflammatory cytokines and ROS, findings that are in some respects mirrored in the results from controlled and epidemiological studies of humans.

15.9.3.2.4 Airway hyperresponsiveness

AHR, as a hallmark of asthma, is an important outcome that has been examined in relation to pollutant exposures. In controlled human exposure studies, inhalation of near-ambient concentrations of ozone for short periods caused increases in non-specific AHR in response to methacholine or histamine challenge. In addition, acute exposure to ozone in combination with common allergens enhanced AHR in asthmatics. In animal studies, acute exposure to ozone in the range of 0.5 to 1 ppm heightened AHR in laboratory animals. There was also a synergistic interaction between acute ozone exposure and allergens such as ovalbumin in evoking inflammatory and pulmonary function responses in experiments with sensitized animals of various species. These studies provide mechanistic support to the findings of ozone-induced exacerbation of AHR in atopic humans with asthma. In both animals and humans, increased AHR persists longer and attenuates more slowly than effects on lung function or respiratory symptoms. AHR has not been widely examined in epidemiological studies, but these experimental findings indicate that acute exposure to ozone can increase AHR, and is expected to result in breathing problems for atopic asthmatics due to airway constriction in response to allergens and other triggers.

15.9.3.2.5 Hospital admissions and emergency room visits

In a large number of population-based epidemiological studies, ozone was consistently associated with hospitalizations for respiratory conditions (total, COPD, asthma) and ERVs for asthma, when potential confounders were accounted for in the analysis. These studies were conducted in cities all over the world, including in Canada and in other countries with ambient ozone levels that are experienced in Canada. In most studies, increases in respiratory hospitalizations and ERVs were most pronounced during the warm season, when ambient ozone levels, time spent outdoors, and building air exchange rates (and hence infiltration) are maximal. In studies summarized in the 1999 Ozone SAD, respiratory hospitalizations were increased by approximately 1% for every 10 ppb 1-h max ozone, and asthma ERVs were increased by 6–8.6% per 10 ppb 1-h max. In these studies, increased risks for total respiratory hospitalizations/ERVs were most pronounced in older adults, whereas those for asthma were primarily limited to children and in some instances working-age adults, perhaps reflecting the age-related prevalence of the conditions underlying these different groupings of medical visits.

15.9.3.2.6 Conclusion for respiratory morbidity

In controlled studies, exposure of healthy adults to ambient levels of ozone for several hours caused a variety of respiratory effects, including symptoms, decrements in lung function, increases in airway resistance and bronchial responsiveness to stimuli, and airway inflammation. With the exception of the effects on AHR, each of these types of effects has been consistently associated with ambient ozone concentrations in epidemiological studies. These

associations were generally robust to adjustment for potential confounders including weather and co-pollutants, and were most pronounced in the warm season, both findings indicating that they were specific to ozone. Ozone also caused alterations in breathing, lung injury and inflammation, and AHR in laboratory animals. In conjunction with the results from controlled human exposure studies, the animal toxicological evidence suggests a biologically plausible sequence(s), beginning with an inflammatory response that irritates the respiratory tract, giving rise to cough, pain that inhibits inspiration, and bronchoconstriction that reduces airflow. The inflammatory response also damages the cells lining the respiratory tract, which increases lung permeability and could lead to lung edema. Impairment of the immune system by ozone would also render people more vulnerable to viral or bacterial infections. These effects, if severe enough, could lead to respiratory dysfunction and a requirement for medical intervention, providing a plausible explanation for the increases in ERVs and hospitalizations for respiratory causes (including asthma) that have been consistently reported in the population-based epidemiology studies. While the increased risks reported for respiratory hospitalizations and for asthma ERVs are modest (on the order of 1% and several % per 10 ppb 1-h max ozone, respectively), nonetheless they demonstrate strength of association, because they show a concentration–response relationship, are statistically significant in most studies, and (since the entire population is exposed) represent large numbers of people and substantial impacts on public health.

The epidemiological associations between ambient ozone and respiratory health endpoints, with support from the human and animal toxicological findings, thus meet several of the criteria for causality, including strength of association, robustness, consistency, biological plausibility, and coherence. In conjunction with the experimental findings of respiratory effects in animals and humans, the overall evidence indicates that there is **a causal relationship** between acute exposure to ambient ozone at current levels and increased respiratory morbidity (including decreased lung function, as well as increases in respiratory symptoms, airway injury and inflammation, and AHR), resulting in increased ERVs and hospitalizations.

15.9.3.3 Cardiovascular Morbidity Associated with Acute Exposure

Short-term exposure of laboratory rodents to ozone causes effects on the cardiovascular system, including reduced heart rate and arterial blood pressure and increased frequency of arrhythmias. Various mechanisms by which ozone may cause cardiovascular effects have been posited with some experimental support, including the release of platelet activating factor from lung epithelium contributing to formation of blood clots; reaction of ozone with ELF components to produce oxysterols and ROS, with subsequent effects on heart or lung cells or on clotting; and indirect effects on vasoconstrictor secretion and neuronal reflexes leading to increased blood pressure and altered heart rate or rhythm. Controlled studies of humans exposed to ozone have not investigated cardiovascular endpoints to any substantial degree.

Cardiovascular hospitalizations were increased in relation to acute ambient ozone in only some population-based epidemiology studies, primarily those where ozone levels were relatively high and during the warm season. In some of the small number of available panel studies, there was an association between short-term exposure to ambient ozone and certain cardiac outcomes (HRV, arrhythmias, MI incidence), but the findings were not always significant and/or the endpoints were more strongly related to other pollutants. These somewhat inconsistent findings contrast with the fairly consistent reports of ozone-related increases in cardiovascular mortality discussed in Section 15.9.3.4.

Hence, while studies in animals indicate that short-term exposure to ozone at relevant levels can affect the cardiovascular system, the available limited epidemiological evidence is somewhat lacking with respect to consistency, robustness and coherence. Overall, the evidence

is **suggestive of a causal relationship** between short-term exposure to ambient ozone and cardiovascular morbidity, though the database is limited and more research is needed to better elucidate the link to cardiac outcomes.

15.9.3.4 Mortality Associated with Acute Exposure

In large numbers of epidemiology studies of various designs, there were positive and (particularly in those of strongest design) statistically significant associations between short-term levels of ambient ozone and total non-accidental or total cardiopulmonary mortality. These associations were observed in cities from all regions of the world, encompassing different climatic regimes, pollutant mixes, and socioeconomic conditions. They were also generally robust to model specifications, including adjustment for co-pollutants, and/or were most pronounced in summer, indicating that they were specific to ozone. Extensive analyses revealed a clear concentration–response relationship between acute exposure to ambient ozone and total mortality that extended to very low concentrations. Associations for cardiovascular and respiratory mortality were also generally positive and often statistically significant, though they were somewhat less consistent, especially for respiratory mortality. This may reflect the reduced statistical power by which to examine cause-specific associations and/or the lack of clarifying information on contributing causes of death (e.g. cardiovascular conditions contributing to deaths from respiratory causes, or vice versa). The evidence for subpopulations that are susceptible to ozone-related mortality was limited, though there is some suggestion of increased risk in people with severe asthma or COPD, or in the elderly.

The respiratory effects of ozone have been much studied in experiments in animals and humans, but the mechanism(s) by which it would cause respiratory deaths is not known, though one can hypothesize that ozone initially induces lung damage, with subsequent inflammation and further lung damage and/or reduced lung function leading to respiratory distress in sensitive groups (e.g. severe asthmatics). With respect to cardiovascular mortality, for which there is more consistent epidemiological evidence, there is only a limited evidence base for cardiovascular effects in animals and essentially none from controlled studies in humans. A variety of direct and indirect mechanisms by which ozone could cause cardiovascular effects have been hypothesized based on animal toxicology findings, and again people with pre-existing cardiac or respiratory diseases would be expected to be more susceptible to at least some of these, but the mechanism by which it may cause cardiovascular deaths is not known.

Hence, while knowledge about the specific mechanisms that underly ozone-related mortality remains relatively limited, there are plausible pathways by which ozone could directly or indirectly increase the risk of death from respiratory or cardiovascular causes. In addition, though there is uncertainty with respect to specific causes of death, the associations with total non-accidental and cardiopulmonary mortality clearly display strength of association, robustness and consistency. Therefore, the overall evidence indicates that there is **likely a causal relationship** between acute exposure to ambient ozone and total non-accidental and cardiopulmonary mortality.

15.9.3.5 Effects Associated with Chronic Exposure

The epidemiological evidence for health effects from long-term exposure to ambient ozone is strongest for seasonal effects on lung function growth in children, observed in several studies as reduced rates of growth-related increase of FEV₁ and/or FVC associated with relatively high summertime levels of ozone. There was also some evidence for ozone-related increases in the risk of asthma development, reported as increases in new onset asthma in subgroups that may spend more time outdoors (male adults, children who play multiple sports) in longitudinal studies. With respect to mortality, a re-analysis of the ACS cohort published in 2000 indicated

that long-term ambient ozone concentrations were associated with increased cardiopulmonary mortality.

For each of these findings, there is some support, albeit quite general, from other lines of evidence. For example, effects on lung function growth, the development of asthma, and cardiopulmonary mortality appear quite plausible in light of the extensive evidence that ozone affects the respiratory system. However, even though these findings have been reported in studies of relatively strong design, for each of them the number of studies is quite small, and there are uncertainties about the possible role of other pollutants in the observed relationship for some of the effects.

In laboratory animals, long-term exposure to ozone caused morphological changes in the respiratory tract, including airway remodelling in the centracinar region in monkeys and nasal hyperplasia and mucous cell metaplasia in the upper respiratory tract of rats. The persistent nature of these structural changes suggests the possibility of corresponding changes in humans in response to chronic ozone exposure. However, it is not known what conditions may be needed to cause such changes, and there is no information relevant to these effects from other lines of evidence.

Overall, the limited available evidence is **suggestive of a causal relationship** between long-term exposure to ambient ozone and each of lung function growth in children, asthma development, respiratory mortality, and morphological changes in the respiratory tract. However, for each of these the database is limited in size and scope, and more research is needed to better elucidate the possible link between chronic exposure to ambient ozone and these health effects.

15.9.3.6 Subgroups with Increased Sensitivity or Exposure to Ambient Ozone

Available evidence indicates that a variety of factors can affect individuals' responses to ambient ozone. Some of these are innate factors that affect the sensitivity of individuals to exposure to ozone, such as certain pre-existing diseases. Other factors may render individuals more vulnerable to ozone by increasing their exposure, for example time-activity patterns.

Individuals with pre-existing respiratory disease may be sensitive to the additional oxidative burden from exposure to ambient ozone, and a number of lines of evidence indicate that asthmatics are a susceptible subgroup. In some controlled human exposure studies, subjects with asthma had ozone-induced increases in spirometric responses and inflammatory responses compared with healthy young adults. Acute experimental exposure to ozone also enhanced AHR in asthmatics in combination with common allergens, and repeated exposure increased AHR in subjects with allergic airway disease (with or without asthma). In laboratory animals, there was a synergistic interaction between acute ozone exposure and allergens such as ovalbumin in evoking inflammatory and lung function responses in sensitized rats, mice and guinea pigs. AHR is the hallmark of asthma, and collectively these results provide a possible explanation for the associations between acute ambient ozone and reduced lung function reported in panel studies, and respiratory hospitalizations and asthma ERVs reported in population-based epidemiology studies.

In contrast to the results for asthmatics, in controlled human exposure studies people with COPD did not have greater ozone-induced changes in lung function than healthy subjects, perhaps because most people with COPD are older and would therefore not be expected to have such changes. However, in a number of population-based epidemiology studies, increases in ERVs, hospitalizations and mortality from COPD were associated with acute ambient ozone concentrations, indicating that people with this condition may be a potentially susceptible subgroup. Though lung function changes are a significant predictor of COPD exacerbation, a

number of other issues, such as co-morbidity, shortness of breath and some socioeconomic factors, play important roles in the worsening of COPD and may complicate the identification of this disease in relation to ozone exposure.

Age-related changes in lung function in response to ozone exposure have been reported, with responsiveness diminishing from young adulthood. Children and older adults also have lesser respiratory symptom responses to ozone exposure than young adults, and may receive increased ozone doses as a consequence of experiencing less severe symptoms. The results of epidemiology studies indicate that children, especially asthmatics, may be more at risk of adverse respiratory health outcomes associated with ambient ozone, including reduced lung function and respiratory symptoms and increased asthma ERVs with acute exposures, as well as reduced lung function growth with seasonal exposure. Older adults also appear to be more sensitive to the acute effects of ozone, evident as increased risks for total respiratory hospitalizations and ERVs, and for mortality. It should be noted that even though the risk estimates for older adults were only slightly higher, the absolute effect of ozone is substantially greater, due to the higher underlying death rates in this age group.

There is emerging evidence that genetics are at least in part responsible for the substantial differences in sensitivity to ozone that exist between individuals. Studies have identified ozone-sensitive and resistant strains of rats and mice that differ in their susceptibility to ozone-induced lung injury and inflammation, illustrating the importance of genetic makeup in determining susceptibility to ozone. Genetic and molecular characterization studies have identified chromosomal loci that contribute to sensitivity or resistance of laboratory animals. Controlled human exposure and panel studies have also shown that genetic polymorphisms of antioxidant enzymes and inflammatory mediators confer differences in sensitivity to ozone-induced effects on pulmonary function and airway inflammation.

Outdoor workers, children, and other individuals that are active outdoors can be more vulnerable to the effects of ozone. This is in part because they are exposed to ambient ozone out of doors, where concentrations are greatest, often during the warm season and at the height of the day, when ozone levels are maximal. People engaged in these activities are also exerting themselves, and it is known from experiments in animals and humans that physical activity enhances exposure and the respiratory effects of ozone. The results of panel studies confirm that ambient ozone is associated with decrements in lung function in children and in workers and other individuals that are active outdoors. Moreover, in epidemiology studies chronic ambient ozone was associated with decreased lung function growth in children and with new onset asthma cases in subgroups that may spend more time outdoors (children engaged in large numbers of sports, male adults).

15.9.4 Shape of the Concentration–Response Curve

The shape of the concentration–response relationship between ambient ozone and various health outcomes has implications for estimating the health impacts from exposure to ambient ozone and for risk management to address these impacts. This aspect of the association between ozone and health effects, including the potential for the existence of threshold levels below which health effects are not observed, has been investigated in a number of studies.

The most extensive analyses have addressed the associations between acute ambient ozone and total non-accidental mortality, for which the data are routinely collected in a standardized fashion and therefore the datasets are the most powerful. In an analysis of the US NMMAPS dataset of many years' data for 98 US cities reviewed in this Assessment, a variety of approaches were used to explore the concentration–response relationship (linear, subset,

threshold, and spline models). The results using all of these approaches (including those that did not make any *a priori* assumptions about the shape of the curve) indicated that mortality was related to ambient ozone in an approximately linear fashion at concentrations greater than 10 ppb 24-h ozone. Only at this level or less was there little evidence of an association, indicating that if a threshold does exist, it is likely close to or below background concentrations. Most other studies that have investigated the shape of the relationship between acute ozone and mortality have also indicated that it is approximately linear, in some instances down to very low concentrations, though this study is the one of strongest design.

Similarly, the shape of the concentration–response function between ozone and respiratory hospitalizations or ERVs has been examined in a number of time-series studies reviewed in previous assessments. In most of these studies, a monotonic increase in the concentration–response function extending down to very low ambient concentrations was reported, and there was no clear evidence of a threshold for ozone-related effects on respiratory admissions or asthma ERVs.

The shape of the concentration–response relationship for other health measures has not been much studied, but the data are generally coherent with the findings for medical visits. In a US multi-city panel study of asthmatic children reviewed in the US EPA 2006 Ozone AQCD, ozone-related decrements in PEF and increases in respiratory symptoms both persisted when using all data available and after restricting the 8-h average ozone concentrations to <80 ppb. In the controlled human exposure study reviewed in this Assessment in which exposure–response was best characterized, there were monotonic decreases in FEV₁ and FVC and similar increases in two measures of symptom response across all concentrations tested (0.04 to 0.08 ppm) compared with filtered air, with no apparent threshold in this concentration range.

It should be noted that the general lack of a clearly identifiable threshold at a population level based on the epidemiology studies is consistent with the wide range of interindividual susceptibility to the respiratory effects of ozone observed in the controlled human exposure studies. Although individual thresholds may exist, they are likely to differ widely, particularly considering that the population-based epidemiological studies, unlike the controlled human exposure studies, include subjects who have the most severe pre-existing disease and are hence most likely to be affected by air pollutants at low concentrations. Due to the large differences in sensitivity that are the result of this heterogeneity within the general population, a common threshold may well not be observable at a population level in epidemiology studies. In addition, a number of the disease conditions that are affected by ozone (e.g. asthma, COPD) are common in the general population and are the combined result of multiple risk factors. If exposure to ozone is exacerbating these diseases, its effects would be expected to be additive to the other factors already contributing to the disease, without exhibiting any evidence of a threshold. However, it is recognized that other factors may also make it difficult to identify a threshold at a population level, including low data density in the lower ozone concentration range, or measurement error resulting from differences between individuals in the relationship between personal exposure to ozone and its ambient concentrations. Regardless of the reasons for the general lack of an evident threshold in the epidemiologic studies, overall the current evidence indicates that if a general population threshold level exists for the health effects of ozone, it is likely near the lower limit of ambient ozone concentrations.

15.9.5 Uncertainties in Assessment of Health Effects of Ozone

A number of uncertainties exist in the relationship between exposure to ambient ozone and health effects. This section discusses a number of the uncertainties in the database that has been used to characterize the risks associated with ambient ozone in this review. Some of these

issues are considered important sources of uncertainty, whereas for some others research results indicate that they are of lesser importance. For each issue discussed, the uncertainties and their implications are briefly summarized.

- *Central site monitoring as a measure of exposure*—Many of the epidemiological studies reviewed rely on a single central monitor, or the averaging of several, to characterize the pollution levels in a given community, using the resultant ozone concentration as an indicator of population exposure. Because ozone exhibits some spatial heterogeneity, both within the airshed at large and between microenvironments, a mismatch of individual exposures and their health status can result. The relationship between ambient concentrations and personal exposure to ambient ozone will vary as a result of individual-, city-, or region-specific differences, resulting in measurement error and potential bias in risk estimates. Bias from exposure misclassification is a concern in any epidemiological analysis. The bias can be either upward or downward, though it is expected to most often underestimate risks and make it more difficult to detect a health effect.

—However, it should be noted that much ambient ozone is the result of broad regional transport, and high correlations are often observed between sites up to 100 km apart. As well, both Canadian and American personal monitoring studies have shown that mean personal exposures are most often significantly related to, and/or follow the same temporal trend as, concentrations at the corresponding central site. This occurs particularly during the warm season, when ozone levels, air exchange rates, and time spent outdoors are highest (this is also the season in which the association of ozone with a range of health effects is most pronounced). These findings suggest that, although data from central monitors do not reflect the individual variation in personal exposure to ozone, they appear to be a reasonable surrogate for the population average exposure to ambient ozone.

—Moreover, much of the epidemiological literature on the health effects of ambient ozone is made up of time-series studies. These studies are less subject to bias due to differences in indoor versus outdoor concentrations within and between microenvironments, variability in daily time-series patterns, and changes in mean exposures over multi-year time spans, than occurs in cross-sectional (spatial) analysis. This is because time-series studies longitudinally examine the variations in exposure that a single population in an urban airshed experiences over a short time, with the population serving as its own control.

—It is also important to keep in mind that epidemiology studies using central site ozone levels as a surrogate for exposure, while they can have considerable measurement error for individual exposures as a result of the factors discussed above, by definition are more likely to yield less biased health risk estimates **associated with ambient ozone** for the population as a whole than for the individual. As well, the risk estimates from such studies will yield the best estimates of the health benefits for the population that will result from specified reductions in ambient ozone concentrations.

- *Role of co-pollutants*—The extent to which co-pollutants may modify or contribute to ozone's health effects can also be an important source of uncertainty. Air pollution is a complex mixture of substances, some of which are often highly correlated with ozone, making it difficult to determine the impact of any single pollutant in the mixture. Nonetheless, in those epidemiology studies of mortality or respiratory morbidity that included analyses with other pollutants in conjunction with ozone, the associations with ozone were often fairly robust to adjustment for one or more of PM, NO₂, SO₂ and CO. In addition, the association of ambient ozone with a range of health effects was frequently most pronounced in the warm season, providing further confidence that these effects are specific to ozone.

—Ozone has long been used as an indicator of the entire photochemical oxidant mix of which it is a part, and the contribution of the other substances in the mix (e.g. H₂O₂, PAN), for which exposure and effects information are largely non-existent, is largely unknown. Limited data for oxidants other than ozone suggest that their gas and particle phase concentrations combined are probably <10% that of ozone.

—Toxicological and controlled human exposure studies have also investigated interactions of simple combinations of ozone and other pollutants. The evidence for interactive effects is limited and inconclusive, and interactions have generally occurred only at higher than ambient concentrations. A finding previously indicated and made more robust by recent data is that interactions occur between ozone, pathogens and aeroallergens. It appears that ozone potentiates the lung with respect to infection and damage by pathogens and also that an interaction with ozone and some allergens leads to AHR. The importance of these reactions in the findings of epidemiological associations with mortality and other endpoints is unclear, but additional research in this area could contribute to a fuller understanding of the effects, and of the importance of pre-existing disease and physiological states.

- *Concentration–response relationships, thresholds*—For those health endpoints associated with ambient ozone in the epidemiological studies, an important question in characterizing risk is the shape of the concentration–response curve, and the issue of potential population threshold levels. Most of the recent studies that have investigated the issue of thresholds continue to show no clear evidence for a threshold in the relationships between ozone concentrations and various health endpoints, including premature mortality, or have suggested that if thresholds exist they must be at very low levels approaching or below background (Section 15.9.4).

—As discussed in Section 15.9.4, the lack of a clear threshold at a population level is consistent with the wide range of interindividual susceptibility to the respiratory effects of ozone observed in the controlled studies in humans. Although individual thresholds may exist, they are probably widely different, particularly considering that the population-based epidemiological studies, unlike the controlled human exposure studies, include subjects who have the most severe pre-existing disease and are hence most likely to be affected by air pollutants at low concentrations. In addition, a number of the disease conditions that are affected by ozone are common in the general population as a result of multiple risk factors, in which case ozone's contribution would be expected to be incremental, without any evidence of a threshold. However, the extent to which exposure errors, misclassification of exposure, or potential impacts of other co-pollutants may mask potential population thresholds is still not known. Greater clarity on the concentration–response relationship at low concentrations would provide useful information, especially in the realm of benefit–cost analysis where the absence of a threshold has significant implications.

- *Cumulative risks of short-term exposures*—The majority of epidemiology studies have reported risk estimates for short-term lags, most often for single days. However, the results of some studies have indicated that risks are greater in relation to longer cumulative periods of several days. These findings suggest that the risk estimates reported in epidemiology studies for lags of an individual day or two underestimate the health risks of ambient ozone.
- *Effects associated with long-term exposures*—While there are some reports that long-term exposure to ambient ozone is associated with health effects, including lung function growth, asthma development, and cardiopulmonary mortality, these findings are based on few studies and require confirmation in other settings. It is noted that chronic effects dominate overall health impacts for PM, which suggests that further research to better define the potential for effects of long-term ozone exposure is warranted. In addition, the exploration of

other time lags, such as summer average, has not featured significantly to date in the epidemiological literature, thus leaving an important gap in the understanding of population-level effects. Work in each of these areas would serve to better define the need for and time-scale of a longer-term ambient standard for ozone.

15.9.6 Conclusions

This concluding section presents a summary of key findings and insights arising from the preceding sections of the risk characterization for ambient ozone. These are presented in point form for various key subject areas, including exposure, the weight of evidence for categories of health effects, subpopulations that are susceptible, and the public health impacts of ozone.

- *Exposure*—The entire population is exposed to ozone of ambient origin. For epidemiological studies, where estimating population average exposure is required, the ambient monitoring system provides an appropriate representation of exposure.
- *Acute Respiratory Morbidity*—Short-term controlled ambient-relevant ozone exposure studies with healthy adults elicited a range of adverse respiratory effects, including respiratory symptoms, decreased lung function, increased AHR, and airway inflammation. Most of these effects were also associated with ambient ozone in epidemiological studies. The mechanisms by which these effects occur have been investigated in both humans and animals and provide biologically plausible pathways to explain these effects.

—Ambient ozone concentrations were positively and robustly associated with increased respiratory hospitalizations and asthma ERVs in numerous population-based epidemiology studies; these findings are strongly supported by the experimental and epidemiological evidence for lung function decrements, increased respiratory symptoms, airway inflammation, and AHR.

—The epidemiological associations with respiratory health endpoints exhibit strength of association, robustness, consistency, biological plausibility, and coherence. In conjunction with the experimental findings in animals and humans, the overall evidence indicates that there is **a causal relationship** between acute exposure to ambient ozone and increased respiratory morbidity (including decreased lung function, as well as increases in respiratory symptoms, airway injury and inflammation, and AHR), resulting in increased asthma ERVs and respiratory hospitalizations.

- *Acute Cardiovascular Morbidity*—Short-term exposure of laboratory rodents to ozone caused effects on the cardiovascular system, including reduced heart rate and blood pressure and increased arrhythmias, and provided experimental support for various plausible mechanisms by which ozone may cause cardiovascular effects.

—Acute exposure to ambient ozone was associated with cardiovascular hospitalizations in only some population-based epidemiology studies and with cardiac endpoints (HRV, arrhythmias, MI incidence) in only some panel studies. These somewhat inconsistent findings contrast with more consistent reports of ozone-related increases in mortality from cardiovascular causes.

—While studies in animals indicate that exposure to ozone at relevant levels can affect the cardiovascular system, the limited epidemiological evidence is somewhat lacking in consistency, robustness and coherence. Overall, the evidence is **suggestive of a causal relationship** between short-term exposure to ozone and cardiovascular morbidity, though the database is limited and more research is needed.

- *Acute Mortality*—In numerous epidemiological studies of various designs, short-term ambient ozone was robustly and specifically associated with total non-accidental or total cardiopulmonary mortality in cities with different climates, pollutant mixes, and socioeconomic conditions. Associations with cardiovascular and respiratory deaths were generally positive and often significant, though somewhat less consistent, especially for respiratory causes.

—Knowledge of the specific mechanisms that may underly ozone-related mortality remains limited, though there are plausible pathways by which it could increase the risk of death from respiratory or cardiovascular causes. While there is uncertainty for specific causes of death, the associations with total non-accidental and cardiopulmonary mortality clearly display strength of association, robustness, and consistency. Therefore, the overall evidence indicates that there is **likely a causal relationship** between acute exposure to ambient ozone and non-accidental and cardiopulmonary mortality.

- *Other Effects*—Overall, the limited available evidence is **suggestive of a causal relationship** between long-term exposure to ambient ozone and each of lung function growth in children, asthma development, respiratory mortality, and morphological changes in the respiratory tract. However, for each of these the database is limited in size and scope, and more research is needed.

—A number of other emerging ozone-related effects warrant further examination, including those on the CNS and on cardiovascular, reproductive, and developmental endpoints, to determine if such effects are consistently observed and occur at relevant concentrations.

- *Subgroups with Increased Sensitivity or Exposure to Ozone*—Individuals with certain pre-existing diseases appear to be sensitive to exposure to ozone. The weight of evidence from controlled human exposure, epidemiological, and animal toxicological studies indicates that asthmatics are a susceptible subgroup. Evidence from epidemiological studies indicates that those with COPD are also more susceptible to the effects of ozone.

—Age can affect the sensitivity to ozone in several respects. Children and older adults have lesser symptom responses to ozone than young adults, and may receive increased exposures as a result of experiencing less severe symptoms. The results of epidemiology studies indicate that children, especially asthmatics, may be more at risk of adverse respiratory health outcomes from ozone exposure. Older adults appear to be more sensitive to acute ozone-related respiratory hospitalizations and ERVs, and mortality.

—Some subgroups have greater exposures to and are more affected by ozone because they spend more time outdoors and/or are active at times when ambient ozone levels are relatively high; these include outdoor workers, children, and other individuals that are active outdoors.

- *Public Health Impacts*—The effects associated with ozone have been observed in epidemiological studies in Canada, as well as in epidemiological studies in other countries or in controlled human exposure studies at ozone concentrations that occur in Canada.

—In most of the studies that examined the shape of the concentration–response relationship for ozone-related mortality or hospitalizations, there was an approximately linear relationship, with no clear evidence for a threshold. The lack of a population threshold is consistent with the large interindividual differences in sensitivity to ozone observed in the experimental human studies, and with the high prevalence and multi-factorial nature of a number of the disease conditions that are associated with ozone. While there are limitations in the ability of epidemiological methods to determine the presence or absence of thresholds of effect, well-conducted studies examining this phenomenon have concluded that population effect

thresholds, should they exist, would be at very low ambient concentrations. Consequently, the available evidence indicates that any increment in anthropogenic concentrations of ozone presents an increased risk for serious health effects, including premature mortality.

—Although the risks for ozone-related health effects are relatively small by traditional epidemiological standards, the entire population is exposed to ambient ozone, and the subpopulations that have increased sensitivity or exposure to ozone (including older adults, children, and individuals with certain common respiratory conditions (asthmatics, COPD)) comprise a considerable proportion of the population. In addition, the serious health impacts that have been the focus of most assessments, including mortality, hospitalizations, and ERVs are just the “tip of the iceberg” in the pyramid of health effects associated with ozone, and the unmeasured morbidity has important public health impacts and costs. As a result, the public health impacts of ambient ozone are substantial, and can only be expected to grow as the population ages and the prevalence of age-related diseases that confer susceptibility to ozone increases. Finally, under the influence of climate change, there are expectations of increasing ozone levels, with the potential for associated increased population health impacts.

15.10 References

- Adams WC. 2006a. Comparison of chamber 6.6-h exposures to 0.04-0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. *Inhal Toxicol* 18:127–136.
- Adams WC. 2006b. Human pulmonary responses with 30-minute time intervals of exercise and rest when exposed for 8 hours to 0.12 ppm ozone via square-wave and acute triangular profiles. *Inhal Toxicol* 18:413–22.
- Ahmad S, Ahmad A, McConville G, Schneider BK, Allen CB, Manzer R, Mason RJ, and White CW. 2005. Lung epithelial cells release ATP during ozone exposure: signaling for cell survival. *Free Radic Biol Med* 39:213–26.
- Alexis NE, Eldridge MW, and Peden DB. 2003. Effect of inhaled endotoxin on airway and circulating inflammatory cell phagocytosis and CD11b expression in atopic asthmatic subjects. *J Allergy Clin Immunol* 112:353–61.
- Alexis NE, Becker S, Bromberg PA, Devlin R, and Peden DB. 2004. Circulating CD11b expression correlates with the neutrophil response and airway mCD14 expression is enhanced following ozone exposure in humans. *Clin Immunol* 111:126–31.
- Alfaro-Rodriguez A and Gonzalez-Pina R. 2005. Ozone-induced paradoxical sleep decrease is related to diminished acetylcholine levels in the medial preoptic area in rats. *Chem Biol Interact* 151:151–8.
- Angoa-Perez M, Jiang H, Rodriguez AI, Lemini C, Levine RA, and Rivas-Arancibia S. 2006. Estrogen counteracts ozone-induced oxidative stress and nigral neuronal death. *Neuroreport* 17:629–33.
- Arjomandi M, Witten A, Abbritti E, Reintjes K, Schmidlin I, Zhai W, Solomon C, and Balmes J. 2005a. Repeated exposure to ozone increases alveolar macrophage recruitment into asthmatic airways. *Am J Respir Crit Care Med* 172:427–32.
- Arjomandi M, Schmidlin I, Girling P, Boylen K, Ferrando R, and Balmes J. 2005b. Sputum induction and bronchoscopy for assessment of ozone-induced airway inflammation in asthma. *Chest* 128:416–23.
- Asplund PT, Ben-Jebria A, Rigas ML, and Ultman JS. 1996. Longitudinal distribution of ozone absorption in the lung: effect of continuous inhalation exposure. *Arch Environ Health* 51:431–8.
- Avol EL, Navidi WC, and Colome SD. 1998a. Modeling ozone levels in and around Southern California homes. *Environ Sci Technol* 32:463–8.
- Avol EL, Navidi WC, Rappaport EB, and Peters JM. 1998b. Acute effects of ambient ozone on asthmatic, wheezy, and healthy children. Boston, MA: Health Effects Institute. Research Report No. 82.
- Ball BA, Folinsbee LJ, Peden DB, and Kehrl HR. 1996. Allergen bronchoprovocation of patients with mild allergic asthma after ozone exposure. *J Allergy Clin Immunol* 98:563–72.
- Ballester F, Rodriguez P, Iniguez C, Saez M, Daponte A, Galan I, Taracido M, Arribas F, Bellido J, Cirarda FB, Canada A, Guillen JJ, Guillen-Grima F, Lopez E, Perez-Hoyos S, Lertxundi A, and Toro S. 2006. Air pollution and cardiovascular admissions association in Spain: results within the EMECAS project. *J Epidemiol Community Health* 60:328–36.

- Ballinger CA, Cueto R, Squadrito G, Coffin JF, Velsor LW, Pryor WA, and Postlethwait EM. 2005. Antioxidant-mediated augmentation of ozone-induced membrane oxidation. *Free Radic Biol Med* 38:515–26.
- Barragan-Mejia MG, Castilla-Serna L, Calderon-Guzman D, Hernandez-Islas JL, Labra-Ruiz NA, Rodriguez-Perez RA, and Angel DS. 2002. Effect of nutritional status and ozone exposure on rat brain serotonin. *Arch Med Res* 33:15–19.
- Bayram H, Rusznak C, Khair OA, Sapsford RJ, and Abdelaziz MM. 2002. Effect of ozone and nitrogen dioxide on the permeability of bronchial epithelial cell cultures of non-asthmatic and asthmatic subjects. *Clin Exp Allergy* 32:1285–92.
- Bell ML. 2006. The use of ambient air quality modeling to estimate individual and population exposure for human health research: A case study of ozone in the Northern Georgia Region of the United States. *Env Int* 32:586–93.
- Bell ML, McDermott A, Zeger SL, Samet JM, and Dominici F. 2004. Ozone and short-term mortality in 95 US urban communities, 1987–2000. *JAMA* 292:2372–8.
- Bell ML, Dominici F, and Samet JM. 2005. A meta-analysis of time-series studies of ozone and mortality with comparison to the national morbidity, mortality, and air pollution study. *Epidemiology* 16:436–45.
- Bell ML, Peng RD, and Dominici F. 2006. The exposure-response curve for ozone and risk of mortality and the adequacy of current ozone regulations. *Environ Health Perspect* 114:532–6.
- Biggeri A, Baccini M, Bellini P, and Terracini B. 2005. Meta-analysis of the Italian studies of short-term effects of air pollution (MISA), 1990–1999. *Int J Occup Environ Health* 11:107–22.
- Black MS. 2006. Printing Systems: Meeting Market Demands for Healthy Indoor Environments. *In: Proc 22nd Int Conf Dig Print Technol*; September 17, 2006; Denver, Colorado. p. 510–13.
- Blondeau P, Iordache V, Poupard O, Genin D, and Allard F. 2005. Relationship between outdoor and indoor air quality in eight French schools. *Indoor Air* 15:2–12.
- Boutin-Forzano S, Adel N, Gratecos L, Jullian H, Garnier JM, Ramadour M, Lanteaume A, Hamon M, Lafay V, and Charpin D. 2004. Visits to the emergency room for asthma attacks and short-term variations in air pollution. A case-crossover study. *Respiration* 71:134–7.
- Brauer M and Brook JR. 1997. Ozone personal exposures and health effects for selected groups residing in the Fraser Valley. *Atmos Env* 31:2113–21.
- Brook RD, Brook JR, Urch B, Vincent R, Rajagopalan S, and Silverman F. 2002. Inhalation of fine particulate air pollution and ozone causes acute arterial vasoconstriction in healthy adults. *Circulation* 105:1534–36.
- Bush ML, Asplund PT, Miles KA, Ben-Jebria A, and Ultman JS. 1996. Longitudinal distribution of O₃ absorption in the lung: gender differences and intersubject variability. *J Appl Physiol* 81:1651–7.
- Campos-Bedolla P, Vargas MH, and Montano LM. 2002. Effect of acute ozone exposure on pregnant rat uterus contractile responses. *Reprod Toxicol* 16:269–73.
- Canada, 2011. Canadian Smog Science Assessment of Fine PM and Ground-Level Ozone.
- Cassee FR, Boere AJ, Fokkens PH, Leseman DL, Sioutas C, Kooter IM, and Dormans JA. 2005. Inhalation of concentrated particulate matter produces pulmonary inflammation and systemic biological effects in compromised rats. *J Toxicol Environ Health A* 68:773–96.

- Chan CC, Chuang KJ, Su TC, and Lin LY. 2005. Association between nitrogen dioxide and heart rate variability in a susceptible population. *Eur J Cardiovasc Prev Rehabil* 12:580–6.
- Chang L-T, Koutrakis P, Catalano PJ, and Suh HH. 2000. Hourly personal exposures to fine particles and gaseous pollutants—Results from Baltimore, Maryland. *J Air Waste Man Assoc* 50:1223–35.
- Chen C, Arjomandi M, Qin H, Balmes J, Tager I, and Holland N. 2006. Cytogenetic damage in buccal epithelia and peripheral lymphocytes of young healthy individuals exposed to ozone. *Mutagenesis* 21:131–7.
- Chen LL, Tager IB, Peden DB, Christian DL, Ferrando RE, Welch BS, and Balmes JR. 2004. Effect of ozone exposure on airway responses to inhaled allergen in asthmatic subjects. *Chest* 125:2328–35.
- Chen W, Zhang JS, and Zhang Z. 2005. *ASHRAE Transactions* 111 Pt I:1101–14.
- Cheng TJ, Kao HP, Chan CC, and Chang WP. 2003. Effects of ozone on DNA single-strand breaks and 8-oxoguanine formation in A549 cells. *Environ Res* 93:279–84.
- Christian DL, Chen LL, Scannell CH, Ferrando RE, Welch BS, and Balmes JR. 1998. Ozone-induced inflammation is attenuated with multiday exposure. *Am J Respir Crit Care Med* 158:532–7.
- Chuang KJ, Chan CC, Shiao GM, and Su TC. 2005. Associations between submicrometer particles exposures and blood pressure and heart rate in patients with lung function impairments. *J Occup Environ Med* 47:1093–8.
- Colin-Barenque L, Dorado-Martinez C, Rivas-Arancibia S, Avila-Costa MR, and Fortoul TI. 2005. Morphological recovery of the granule cells from the olfactory bulb after the cessation of acute ozone exposure. *Int J Neurosci* 115:411–21.
- Dales R, Burnett RT, Smith-Doiron M, Stieb DM, and Brook JR. 2004. Air pollution and sudden infant death syndrome. *Pediatrics* 113:e628–31.
- Delfino RJ, Coate BD, Zeiger RS, Seltzer JM, Street DH, and Koutrakis P. 1996. Daily asthma severity in relation to personal ozone exposure and outdoor fungal spores. *Am J Respir Crit Care Med* 154:633–41.
- Delfino RJ, Zeiger RS, Seltzer JM, Street DH, and McLaren CE. 2002. Association of asthma symptoms with peak particulate air pollution and effect modification by anti-inflammatory medication use. *Environ Health Perspect* 110:A607–17.
- Delfino RJ, Staimer N, Gillen D, Tjoa T, Sioutas C, Fung K, George SC, and Kleinman MT. 2006. Personal and ambient air pollution is associated with increased exhaled nitric oxide in children with asthma. *Environ Health Perspect* 114:1736–43.
- DeLorme MP, Yang H, Elbon-Copp C, Gao X, Barraclough-Mitchell H, and Bassett DJ. 2002. Hyperresponsive airways correlate with lung tissue inflammatory cell changes in ozone-exposed rats. *J Toxicol Environ Health A* 65:1453–70.
- Diaz J, Linares C, Garcia-Herrera R, Lopez C, and Trigo R. 2004. Impact of temperature and air pollution on the mortality of children in Madrid. *J Occup Environ Med* 46:768–74.
- Diaz-Llera S, Gonzalez-Hernandez Y, Prieto-Gonzalez EA, and Azoy A. 2002. Genotoxic effect of ozone in human peripheral blood leukocytes. *Mutat Res* 517:13–20.
- Dockery DW, Luttmann-Gibson H, Rich DQ, Link MS, Mittleman MA, Gold DR, Koutrakis P, Schwartz JD, and Verrier RL. 2005. Association of air pollution with increased incidence of

ventricular tachyarrhythmias recorded by implanted cardioverter defibrillators. *Environ Health Perspect* 113:670–4.

Dubowsky SD, Suh H, Schwartz J, Coull BA, and Gold DR. 2006. Diabetes, obesity, and hypertension may enhance associations between air pollution and markers of systemic inflammation. *Environ Health Perspect* 114:992–8.

Dugandzic R, Dodds L, Stieb D, and Smith-Doiron M. 2006. The association between low level exposures to ambient air pollution and term low birth weight: a retrospective cohort study. *Environ Health* 5:3.

Environment Canada. 2011. Canadian Smog Science Assessment. Final Supporting Document. Volume 1. Atmospheric Science and Environmental Effects. Available upon request from _____.

Escalante-Membrillo C, Gonzalez-Maciuel A, Reynoso-Robles R, and Gonzalez-Pina R. 2005. Brain thiobarbituric acid-reactive substances in rats after short periods of ozone exposure. *Environ Res* 99:68–71.

Fakhrzadeh L, Laskin JD, and Laskin DL. 2002. Deficiency in inducible nitric oxide synthase protects mice from ozone-induced lung inflammation and tissue injury. *Am J Respir Cell Mol Biol* 26:413–9.

Fakhrzadeh L, Laskin JD, Gardner CR, and Laskin DL. 2004a. Superoxide dismutase-overexpressing mice are resistant to ozone-induced tissue injury and increases in nitric oxide and tumor necrosis factor-alpha. *Am J Respir Cell Mol Biol* 30:280–7.

Fakhrzadeh L, Laskin JD, and Laskin DL. 2004b. Ozone-induced production of nitric oxide and TNF-alpha and tissue injury are dependent on NF-kappaB p50. *Am J Physiol Lung Cell Mol Physiol* 287:L279–85.

Fanucchi MV, Plopper CG, Evans MJ, Hyde DM, Van Winkle LS, Gershwin LJ, and Schelegle ES. 2006. Cyclic exposure to ozone alters distal airway development in infant rhesus monkeys. *Am J Physiol Lung Cell Mol Physiol* 291:L644–50.

Farhat SC, Paulo RL, Shimoda TM, Conceicao GM, Lin CA, Braga AL, Warth MP, and Saldiva PH. 2005. Effect of air pollution on pediatric respiratory emergency room visits and hospital admissions. *Braz J Med Biol Res* 38:227–35.

Feng R, He W, Ochi H, and Castranova V. 2006. Ozone exposure impairs antigen-specific immunity but activates IL-7-induced proliferation of CD4-CD8- thymocytes in BALB/c mice. *J Toxicol Environ Health A* 69:1511–26.

Ferng SF. 2002. Ozone-induced DNA single strand-breaks in guinea pig tracheobronchial epithelial cells in vivo. *Inhal Toxicol* 14:621–33.

Fischer P, Hoek G, Brunekreef B, Verhoeff A, and van Wijnen J. 2003. Air pollution and mortality in The Netherlands: are the elderly more at risk? *Eur Respir J Suppl* 40:34s–38s.

Forastiere F, Stafoggia M, Picciotto S, Bellander T, D'Ippoliti D, Lanki T, von Klot S, Nyberg F, Paatero P, Peters A, Pekkanen J, Sunyer J, and Perucci CA. 2005. A case-crossover analysis of out-of-hospital coronary deaths and air pollution in Rome, Italy. *Am J Respir Crit Care Med* 172:1549–55.

Foucaud L, Bennisroune A, Klestadt D, Laval-Gilly P, and Falla J. 2006. Oxidative stress induction by short time exposure to ozone on THP-1 cells. *Toxicology in Vitro* 20:101–8.

Fu L, Kaneko T, Ikeda H, Nishiyama H, Suzuki S, Okubo T, Trevisani M, Geppetti P, and Ishigatsubo Y. 2002. Tachykinins via Tachykinin NK(2) receptor activation mediate ozone-

induced increase in the permeability of the tracheal mucosa in guinea-pigs. *Br J Pharmacol* 135:1331–5.

Funabashi H, Shima M, Kuwaki T, Hiroshima K, and Kuriyama T. 2004. Effects of repeated ozone exposure on pulmonary function and bronchial responsiveness in mice sensitized with ovalbumin. *Toxicology* 204:75–83.

Geyh AS, Xue J, Özkaynak H, and Spengler JD. 2000. The Harvard Southern California Chronic Ozone Exposure Study: Assessing ozone exposure of grade-school-age children in two Southern California communities. *Environ Health Perspect* 108:265–70.

Gilboa SM, Mendola P, Olshan AF, Langlois PH, Savitz DA, Loomis D, Herring AH, and Fixler DE. 2005. Relation between ambient air quality and selected birth defects, seven county study, Texas, 1997–2000. *Am J Epidemiol* 162:238–52.

Giovannelli L, Pitozzi V, Moretti S, Boddi V, and Dolara P. 2006. Seasonal variations of DNA damage in human lymphocytes: correlation with different environmental variables. *Mutat Res* 593:143–152.

Girardot SP, Ryan PB, Smith SM, Davis WT, Hamilton CB, Obenour RA, Renfro JR, Tromatore KA, and Reed GD. 2006. Ozone and PM_{2.5} exposure and acute pulmonary health effects: a study of hikers in the Great Smoky Mountains National Park. *Environ Health Perspect* 114:1044–52.

Gonzalez-Pina R and Alfaro-Rodriguez A. 2003. Ozone exposure alters 5-hydroxy-indole-acetic acid contents in dialysates from dorsal raphe and medial preoptic area in freely moving rats. Relationships with simultaneous sleep disturbances. *Chem Biol Interact* 146:147–56.

Gonzalez-Pina R, Alfaro-Rodriguez A, Castorena-Maldonado A, and Morales Martinez JJ. 2002. Acute orogastric administration of alpha-tocopherol protects from ozone-induced changes in rat striatal catecholamine levels. *Proc West Pharmacol Soc* 45:59–61.

Gonzalez-Pina R, Alfaro-Rodriguez A, and Morales-Martinez Jde J. 2003. The role of the dorsal raphe in the sleep disruptions produced by ozone exposure. *Proc West Pharmacol Soc* 46:116–20.

Gunnison AF and Hatch GE. 1999. O₃-induced inflammation in pre-pregnant, pregnant, and lactating rats correlates with O₃ dose estimated by ¹⁸O₃. *Am J Physiol* 276:L332–40.

Hanania NA, Tarlo SM, Silverman F, Urch B, Senathirajah N, Zamel N, and Corey P. 1998. Effect of exposure to low levels of ozone on the response to inhaled allergen in allergic asthmatic patients. *Chest* 114:752–756.

Hansen C, Neller A, Williams G, and Simpson R. 2006. Maternal exposure to low levels of ambient air pollution and preterm birth in Brisbane, Australia. *BJOG* 113:935–41.

Harkema JR and Wagner JG. 2005. Epithelial and inflammatory responses in the airways of laboratory rats coexposed to ozone and biogenic substances: enhancement of toxicant-induced airway injury. *Exp Toxicol Pathol* 57 Suppl 1:129–41.

Hatch GE, Slade R, Harris LP, McDonnell WF, Devlin RB, Koren HS, Costa DL, and McKee J. 1994. Ozone dose and effect in humans and rats: a comparison using oxygen-¹⁸ labeling and bronchoalveolar lavage. *Am J Respir Crit Care Med* 150:676–83.

Hathout EH, Beeson WL, Nahab F, Rabadi A, Thomas W, and Mace JW. 2002. Role of exposure to air pollutants in the development of type 1 diabetes before and after 5 years of age. *Pediatr Diabetes* 3:184–8.

- Hathout EH, Beeson WL, Ischander M, Rao R, and Mace JW. 2006. Air pollution and type 1 diabetes in children. *Pediatr Diabetes* 7:81–7.
- Hazucha MJ, Folinsbee LJ, and Seal E Jr. 1992. Effects of steady-state and variable ozone concentration profiles on pulmonary function. *Am Rev Respir Dis* 146:1487–93.
- Hazucha MJ, Folinsbee LJ, and Bromberg PA. 2003. Distribution and reproducibility of spirometric response to ozone by gender and age. *J Appl Physiol* 95:1917–25.
- Health Canada and Environment Canada. 1999. National Ambient Air Quality Objectives for Ground-Level Ozone: Science Assessment Document. Ottawa, ON. Cat. No. En42-17/7-1-1999E.
- HEI (Health Effects Institute). 2003. Revised analyses of time-series studies of air pollution and health. Special Report, Health Effects Institute. Boston, MA.
- Hinwood AL, De Klerk N, Rodriguez C, Jacoby P, Runnion T, Rye P, Landau L, Murray F, Feldwick M, and Spickett J. 2006. The relationship between changes in daily air pollution and hospitalizations in Perth, Australia 1992–1998: a case-crossover study. *Int J Environ Health Res* 16:27–46.
- Hisham MWM and Grosjean D. 1991. Sulfur dioxide, hydrogen sulfide, total reduced sulfur, chlorinated hydrocarbons and photochemical oxidants in Southern California museums. *Atmos Env* 25A:1497–1505.
- Hollingsworth JW 2nd, Cook DN, Brass DM, Walker JK, Morgan DL, Foster WM, and Schwartz DA. 2004. The role of Toll-like receptor 4 in environmental airway injury in mice. *Am J Respir Crit Care Med* 170:126–32.
- Hollingsworth JW 2nd, Cook DN, Brass DM, Walker JK, Morgan DL, Foster WM, and Schwartz DA. 2004. The role of Toll-like receptor 4 in environmental airway injury in mice. *Am J Respir Crit Care Med* 170:126–32.
- Hong YC, Lee JT, Kim H, and Kwon HJ. 2002. Air pollution: a new risk factor in ischemic stroke mortality. *Stroke* 33:2165–9.
- Huen K, Gunn L, Duramad P, Jeng M, Scalf R, and Holland N. 2006. Application of a geographic information system to explore associations between air pollution and micronucleus frequencies in African American children and adults. *Environ Mol Mutagen* 47:236–46.
- Huffman LJ, Prugh DJ, Brumbaugh K, and Ding M. 2002. Influence of hyperthyroidism on rat lung cytokine production and nuclear factor-kappaB activation following ozone exposure. *Inhal Toxicol* 14:1161–74.
- Huffman LJ, Beighley CM, Frazer DG, McKinney WG, and Porter DW. 2006a. Increased susceptibility of hyperthyroid rats to ozone: early events and mechanisms. *J Toxicol Environ Health A* 69:465–79.
- Huffman LJ, Beighley CM, Frazer DG, McKinney WG, and Porter DW. 2006b. Increased susceptibility of the lungs of hyperthyroid rats to oxidant injury: specificity of effects. *Toxicology* 225:119–27.
- Iijima MK and Kobayashi T. 2004. Nasal allergy-like symptoms aggravated by ozone exposure in a concentration-dependent manner in guinea pigs. *Toxicology* 199:73–83.
- Ito K, De Leon S, Thurston GD, Nadas A, and Lippmann M. 2005a. Monitor-to-monitor temporal correlation of air pollution in the contiguous US. *J Expo Analysis Environ Epidemiol* 15:172–84.

- Ito K, De Leon SF, and Lippmann M. 2005b. Associations between ozone and daily mortality: analysis and meta-analysis. *Epidemiology* 16:446–57.
- Ito K, Inoue S, Hiraku Y, and Kawanishi S. 2005c. Mechanism of site-specific DNA damage induced by ozone. *Mutat Res* 585:60–70.
- Jakubowski K, Jedlinska-Krakowska M, and Siwicki AK. 2004. The level of some acute phase proteins, total protein, gamma-globulins and activity of lysozyme in blood plasma of rats supplemented with vitamin E and exposed to ozone. *Pol J Vet Sci* 7:283–7.
- Jang AS, Choi IS, Kim SW, Song BC, Yeum CH, and Jung JY. 2003a. Airway obstruction after acute ozone exposure in BALB/c mice using barometric plethysmography. *Korean J Intern Med* 18:1–5.
- Jang AS, Choi IS, and Lee JU. 2003b. Neuronal nitric oxide synthase is associated with airway obstruction in BALB/c mice exposed to ozone. *Respiration* 70:95–9.
- Jang AS, Choi IS, Lee JU, Park SW, Lee JH, and Park CS. 2004. Changes in the expression of NO synthase isoforms after ozone: the effects of allergen exposure. *Respir Res* 5:5.
- Jang AS, Choi IS, Takizawa H, Rhim T, Lee JH, Park SW, and Park CS. 2005a. Additive effect of diesel exhaust particulates and ozone on airway hyperresponsiveness and inflammation in a mouse model of asthma. *J Korean Med Sci* 20:759–63.
- Jang AS, Choi IS, Yang SY, Kim YG, Lee JH, Park SW, and Park CS. 2005b. Antioxidant responsiveness in BALB/c mice exposed to ozone. *Respiration* 72:79–84.
- Jang AS, Choi IS, Lee JH, Park CS, and Park CS. 2006. Prolonged ozone exposure in a murine model of asthma: adaptation of airway responsiveness and airway remodeling. *Respir Res* 7:24.
- Janic B, Umstead TM, Phelps DS, and Floros J. 2003. An *in vitro* cell model system for the study of the effects of ozone and other gaseous agents on phagocytic cells. *J Immunol Methods* 272:125–34.
- Janic B, Umstead TM, Phelps DS, and Floros J. 2005. Modulatory effects of ozone on THP-1 cells in response to SP-A stimulation. *Am J Physiol Lung Cell Mol Physiol* 288:L317–25.
- Jedlinska-Krakowska M, Bomba G, Jakubowski K, Rotkiewicz T, Jana B, and Penkowski A. 2006a. Impact of oxidative stress and supplementation with vitamins E and C on testes morphology in rats. *J Reprod Dev* 52:203–9.
- Jedlinska-Krakowska M, Gizejewski Z, Dietrich GJ, Jakubowski K, Glogowski J, and Penkowski A. 2006b. The effect of increased ozone concentrations in the air on selected aspects of rat reproduction. *Pol J Vet Sci* 9:11–16.
- Jo W-K and Park J-H. 2005. Characteristics of roadside air pollution in Korean metropolitan city (Daegu) over last 5 to 6 years: Temporal variations, standard exceedances, and dependence on meteorological conditions. *Chemosphere* 59:1557–73.
- Joad JP, Kott KS, Bric JM, Peake JL, Plopper CG, Schelegle ES, Gershwin LJ, and Pinkerton KE. 2006. Structural and functional localization of airway effects from episodic exposure of infant monkeys to allergen and/or ozone. *Toxicol Appl Pharmacol* 214:237–43.
- Johnson T. 1997. A pilot study in Los Angeles to measure personal ozone exposures during scripted activities. Washington, DC: American Petroleum Institute. Publication No. DR 218.
- Johnston CJ, Holm BA, and Finkelstein JN. 2004. Differential proinflammatory cytokine responses of the lung to ozone and lipopolysaccharide exposure during postnatal development. *Exp Lung Res* 30:599–614.

- Johnston CJ, Holm BA, and Finkelstein JN. 2005. Sequential exposures to ozone and lipopolysaccharide in postnatal lung enhance or inhibit cytokine responses. *Exp Lung Res* 31:431–47.
- Johnston CJ, Holm BA, Gelein R, and Finkelstein JN. 2006. Postnatal lung development: immediate-early gene responses post ozone and LPS exposure. *Inhal Toxicol* 18:875–83.
- Johnston RA, Mizgerd JP, and Shore SA. 2005a. CXCR2 is essential for maximal neutrophil recruitment and methacholine responsiveness after ozone exposure. *Am J Physiol Lung Cell Mol Physiol* 288:L61–7.
- Johnston RA, Schwartzman IN, Flynt L, and Shore SA. 2005b. Role of interleukin-6 in murine airway responses to ozone. *Am J Physiol Lung Cell Mol Physiol* 288:L390–7.
- Johnston RA, Theman TA, and Shore SA. 2006. Augmented responses to ozone in obese carboxypeptidase E-deficient mice. *Am J Physiol Regul Integr Comp Physiol* 290:R126–33.
- Jonsson LM, Edlund T, Marklund SL, and Sandstrom T. 2002. Increased ozone-induced airway neutrophilic inflammation in extracellular-superoxide dismutase null mice. *Respir Med* 96:209–14.
- Kafoury RM and Kelley J. 2005. Ozone enhances diesel exhaust particles (DEP)-induced interleukin-8 (IL-8) gene expression in human airway epithelial cells through activation of nuclear factors- kappaB (NF-kappaB) and IL-6 (NF-IL6). *Int J Environ Res Public Health* 2:403–10.
- Kari F, Hatch G, Slade R, Crissman K, Simeonova PP, and Luster M. 1997. Dietary restriction mitigates ozone-induced lung inflammation in rats: a role for endogenous antioxidants. *Am J Respir Cell Mol Biol* 17:740–7.
- Kenyon NJ, van der Vliet A, Schock BC, Okamoto T, McGrew GM, and Last JA. 2002. Susceptibility to ozone-induced acute lung injury in iNOS-deficient mice. *Am J Physiol Lung Cell Mol Physiol* 282:L540–5.
- Kenyon NJ, Last MS, Eiserich JP, Morrissey BM, Temple LM, and Last JA. 2006. Differentiation of the roles of NO from airway epithelium and inflammatory cells in ozone-induced lung inflammation. *Toxicol Appl Pharmacol* 215:250–9.
- Kierstein S, Poulain FR, Cao Y, Grous M, Mathias R, Kierstein G, Beers MF, Salmon M, Panettieri RA Jr, and Haczku A. 2006. Susceptibility to ozone-induced airway inflammation is associated with decreased levels of surfactant protein D. *Respir Res* 7:85.
- Kim MY, Kim HW, Park JH, Kim JS, Jin H, Moon SH, Eu KJ, Cho HS, Kang G, Kim YS, Kim YC, Kim HY, Lee KH, and Cho MH. 2004. Molecular analysis of hprt mutation in B6C3F1 mice exposed to ozone alone and combined treatment of 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone and/or dibutyl phthalate for 32 and 52 weeks. *J Vet Sci* 5:379–85.
- Kleinman MT and Phalen RF. 2006. Toxicological interactions in the respiratory system after inhalation of ozone and sulfuric acid aerosol mixtures. *Inhal Toxicol* 18:295–303.
- Kleinman MT, Hyde DM, Bufalino C, Basbaum C, Bhalla DK, and Mautz WJ. 2003. Toxicity of chemical components of fine particles inhaled by aged rats: effects of concentration. *J Air Waste Manag Assoc* 53:1080–7.
- Klestadt D, Laval-Gilly P, and Falla J. 2002. Ozone-mediated cytotoxicity after short-term exposure and its relation to the production of cellular metabolites (NO, H₂O₂). *Cell Biol Toxicol* 18:259–69.

- Klestadt D, Laval-Gilly P, Foucaud L, and Falla J. 2004. Modification of membrane markers on THP-1 cells after ozone exposure in the presence or absence of fMLP. *Toxicol in Vitro* 18:279–83.
- Klestadt D, Laval-Gilly P, Foucaud L, and Falla J. 2005. Influences of ozone exposure upon macrophage responsiveness to N-formyl-methionyl-leucyl-phenylalanine: Mobility and metabolic changes. *Toxicol in Vitro* 19:199–206.
- Koike E and Kobayashi T. 2004. Ozone exposure enhances antigen-presenting activity of interstitial lung cells in rats. *Toxicology* 196:217–27.
- Koike E, Watanabe H, and Kobayashi T. 2004. Exposure to ozone enhances antigen-presenting activity concentration dependently in rats. *Toxicology* 197:37–46.
- Kongtip P, Thongsuk W, Yoosook W, and Chantanakul S. 2006. Health effects of metropolitan traffic-related air pollutants on street vendors. *Atmosph Environ* 40:7138–45.
- Korrick SA, Neas LM, Dockery DW, Gold DR, Allen GA, Hill LB, Kimball KD, Rosner BA, and Speizer FE. 1998. Effects of ozone and other pollutants on the pulmonary function of adult hikers. *Environ Health Perspect* 106:93–99.
- Koutrakis P, Suh HH, Sarnat JA, Brown KW, Coull BA, and Schwartz J. 2005. Characterization of Particulate and Gas Exposures of Sensitive Subpopulations Living in Baltimore and Boston. Boston, MA: Health Effects Institute. Research Report No. 131.
- Krewski D, Burnett RT, Goldberg MS, Hoover K, Siemiatycki J, Jerrett M, Abramowicz M, and White WH. 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.
- Kumarathasan P, Blais E, Goegan P, Yagminas A, Guenette J, Adamson IY, Crapo JD, Mason RJ, and Vincent R. 2005. 90-day repeated inhalation exposure of surfactant Protein-C/tumor necrosis factor-alpha, (SP-C/TNF-alpha) transgenic mice to air pollutants. *Int J Toxicol* 24:59–67.
- Lagorio S, Forastiere F, Pistelli R, Iavarone I, Michelozzi P, Fano V, Marconi A, Ziemacki G, and Ostro BD. 2006. Air pollution and lung function among susceptible adult subjects: a panel study. *Environ Health* 5:11.
- Larini A and Bocci V. 2005. Effects of ozone on isolated peripheral blood mononuclear cells. *Toxicol in Vitro* 19:55–61.
- Larini A, Bianchi L, and Bocci V. 2003. The ozone tolerance: I) Enhancement of antioxidant enzymes is ozone dose-dependent in Jurkat cells. *Free Radic Res* 37:1163–8.
- Laskin DL, Fakhrzadeh L, Heck DE, Gerecke D, and Laskin JD. 2002. Upregulation of phosphoinositide 3-kinase and protein kinase B in alveolar macrophages following ozone inhalation. Role of NF-kappaB and STAT-1 in ozone-induced nitric oxide production and toxicity. *Mol Cell Biochem* 234–235:91–8.
- Last JA, Ward R, Temple L, and Kenyon NJ. 2004. Ovalbumin-induced airway inflammation and fibrosis in mice also exposed to ozone. *Inhal Toxicol* 16:33–43.
- Last JA, Gohil K, Mathrani VC, and Kenyon NJ. 2005. Systemic responses to inhaled ozone in mice: cachexia and down-regulation of liver xenobiotic metabolizing genes. *Toxicol Appl Pharmacol* 208:117–26.
- Lee K, Vallarino J, Dumyahn T, Özkaynak H, and Spengler JD. 1999. Ozone decay rates in residences. *J Air Waste Man Assoc* 49:1238–44.

- Lee K, Xue J, Geyh AS, Özkaynak H, Leaderer BP, Weschler CJ, and Spengler JD. 2002. Nitrous acid, nitrogen dioxide, and ozone concentrations in residential environments. *Environ Health Perspect* 110:145–9.
- Lee K, Parkhurst WJ, Xue J, Ozkaynak AH, Neuberger D, and Spengler JD. 2004. Outdoor/indoor/personal ozone exposures of children in Nashville, Tennessee. *J Air Waste Man Assoc* 54:352–9.
- Lee YK, Mok Kim S, and Han S. 2003. Ozone-induced inactivation of antioxidant enzymes. *Biochimie* 85:947–52.
- Levy JI, Chemerynski SM, and Sarnat JA. 2005. Ozone exposure and mortality: an empiric bayes metaregression analysis. *Epidemiology* 16:458–68.
- Li YF, Gauderman WJ, Avol E, Dubeau L, and Gilliland FD. 2006. Associations of tumor necrosis factor G-308A with childhood asthma and wheezing. *Am J Respir Crit Care Med* 173:970–6.
- Lin CA, Amador Pereira LA, de Souza Conceicao GM, Kishi HS, Milani R Jr, Ferreira Braga AL, and Nascimento Saldiva PH. 2003. Association between air pollution and ischemic cardiovascular emergency room visits. *Environ Res* 92:57–63.
- Lin CM, Li CY, Yang GY, and Mao IF. 2004. Association between maternal exposure to elevated ambient sulfur dioxide during pregnancy and term low birth weight. *Environ Res* 96:41–50.
- Lipsett MJ, Tsai FC, Roger L, Woo M, and Ostro BD. 2006. Coarse particles and heart rate variability among older adults with coronary artery disease in the Coachella Valley, California. *Environ Health Perspect* 114:1215–20.
- Liu L-JS, Koutrakis P, Leech J, and Broder I. 1995. Assessment of ozone exposures in the greater metropolitan Toronto area. *J Air Waste Man Assoc* 45:223–34.
- Liu L-JS, Delfino R, and Koutrakis P. 1997. Ozone exposure assessment in a Southern California community. *Environ Health Perspect* 105:58–65.
- Liu S, Krewski D, Shi Y, Chen Y, and Burnett RT. 2003. Association between gaseous ambient air pollutants and adverse pregnancy outcomes in Vancouver, Canada. *Environ Health Perspect* 111:1773–8.
- Loupa G, Charpantidou E, Kioutsioukis I, and Rapsomanikis S. 2006. Indoor microclimate, ozone and nitrogen oxides in two medieval churches in Cyprus. *Atmos Env* 40:7457–66.
- Lu FL, Johnston RA, Flynt L, Theman TA, Terry RD, Schwartzman IN, Lee A, and Shore SA. 2006. Increased pulmonary responses to acute ozone exposure in obese db/db mice. *Am J Physiol Lung Cell Mol Physiol* 290:L856–65.
- Luttmann-Gibson H, Suh HH, Coull BA, Dockery DW, Sarnat SE, Schwartz J, Stone PH, and Gold DR. 2006. Short-term effects of air pollution on heart rate variability in senior adults in Steubenville, Ohio. *J Occup Environ Med* 48:780–8.
- Mannes T, Jalaludin B, Morgan G, Lincoln D, Sheppard V, and Corbett S. 2005. Impact of ambient air pollution on birth weight in Sydney, Australia. *Occup Environ Med* 62:524–30.
- Manzer R, Wang J, Nishina K, McConville G, and Mason RJ. 2006. Alveolar epithelial cells secrete chemokines in response to IL-1 β and lipopolysaccharide but not to ozone. *Am J Respir Cell Mol Biol* 34:158–66.

- McConnell R, Berhane K, Yao L, Lurmann FW, Avol E, and Peters JM. 2006. Predicting residential ozone deficits from nearby traffic. *Sci Total Env* 363:166–74.
- Medina-Ramon M, Zanobetti A, and Schwartz J. 2006. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: a national multicity study. *Am J Epidemiol* 163:579–88.
- Michalec L, Choudhury BK, Postlethwait E, Wild JS, Alam R, Lett-Brown M, and Sur S. 2002. CCL7 and CXCL10 orchestrate oxidative stress-induced neutrophilic lung inflammation. *J Immunol* 168:846–52.
- Miller FJ. 1995. Uptake and fate of ozone in the respiratory tract. *Toxicol Lett* 82–83:277–85.
- Molhave L, Kjaergaard SK, Sigsgaard T, and Lebowitz M. 2005. Interaction between ozone and airborne particulate matter in office air. *Indoor Air* 15:383–92.
- Montuschi P, Nightingale JA, Kharitonov SA, and Barnes PJ. 2002. Ozone-induced increase in exhaled 8-isoprostane in healthy subjects is resistant to inhaled budesonide. *Free Radic Biol Med* 33:1403–8.
- Morrison D, Rahman I, and MacNee W. 2006. Permeability, inflammation and oxidant status in airspace epithelium exposed to ozone. *Respir Med* 100:2227–34.
- Mudway IS, Behndig AF, Helleday R, Pourazar J, Frew AJ, Kelly FJ, and Blomberg A. 2006. Vitamin supplementation does not protect against symptoms in ozone-responsive subjects. *Free Radic Biol Med* 40:1702–12.
- Nadadur SS, Costa DL, Slade R, Silbjoris R, and Hatch GE. 2005. Acute ozone-induced differential gene expression profiles in rat lung. *Environ Health Perspect* 113:1717–22.
- National Toxicology Program. 1994. NTP Toxicology and Carcinogenesis Studies of Ozone (CAS No. 10028-15-6) and Ozone/NNK (CAS No. 10028-15-6/ 64091-91-4) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). *Natl Toxicol Program Tech Rep Ser* 440:1–314.
- Nodelman V and Ultman JS. 1999. Longitudinal distribution of chlorine absorption in human airways: a comparison to ozone absorption. *J Appl Physiol* 87:2073–80.
- Otto-Knapp R, Jurgovsky K, Schierhorn K, and Kunkel G. 2003. Antioxidative enzymes in human nasal mucosa after exposure to ozone. Possible role of GSTM1 deficiency. *Inflamm Res* 52:51–5.
- Overton J H and Graham RC. 1989. Predictions of ozone absorption in human lungs from newborn to adult. *Health Physics* 57 Suppl 1:29–36.
- Oyarzun M, Dussaubat N, and Gonzalez S. 2005. Effect of 0.25 ppm ozone exposure on pulmonary damage induced by bleomycin. *Biol-Res* 38:353–8.
- Pacini S, Giovannelli L, Gulisano M, Peruzzi B, Polli G, Boddi V, Ruggiero M, Bozzo C, Stomeo F, Fenu G, Pezzatini S, Pitozzi V, and Dolara P. 2003. Association between atmospheric ozone levels and damage to human nasal mucosa in Florence, Italy. *Environ Mol Mutagen* 42:127–35.
- Park H, Lee B, Ha EH, Lee JT, Kim H, and Hong YC. 2002. Association of air pollution with school absenteeism due to illness. *Arch Pediatr Adolesc Med* 156:1235–9.
- Park JW, Taube C, Joetham A, Takeda K, Kodama T, Dakhama A, McConville G, Allen CB, Sfyroera G, Shultz LD, Lambris JD, Giclas PC, Holers VM, and Gelfand EW. 2004a. Complement activation is critical to airway hyperresponsiveness after acute ozone exposure. *Am J Respir Crit Care Med* 169:726–32.

- Park JW, Taube C, Swasey C, Kodama T, Joetham A, Balhorn A, Takeda K, Miyahara N, Allen CB, Dakhama A, Kim SH, Dinarello CA, and Gelfand EW. 2004b. Interleukin-1 receptor antagonist attenuates airway hyperresponsiveness following exposure to ozone. *Am J Respir Cell Mol Biol* 30:830–6.
- Park JW, Lim YH, Kyung SY, An CH, Lee SP, Jeong SH, and Ju YS. 2005. Effects of ambient particulate matter on peak expiratory flow rates and respiratory symptoms of asthmatics during Asian dust periods in Korea. *Respirology* 10:470–6.
- Park SK, O'Neill MS, Wright RO, Hu H, Vokonas PS, Sparrow D, Suh H, and Schwartz J. 2006. HFE genotype, particulate air pollution, and heart rate variability: a gene-environment interaction. *Circulation* 114:2798–805.
- Parodi S, Vercelli M, Garrone E, Fontana V, and Izzotti A. 2005. Ozone air pollution and daily mortality in Genoa, Italy between 1993 and 1996. *Public Health* 119:844–50.
- Peacock JL, Symonds P, Jackson P, Bremner SA, Scarlett JF, Strachan DP, and Anderson HR. 2003. Acute effects of winter air pollution on respiratory function in schoolchildren in southern England. *Occup Environ Med* 60:82–9.
- Peluso M, Munnia A, Hoek G, Krzyzanowski M, Veglia F, Airoidi L, Autrup H, Dunning A, Garte S, Hainaut P, Malaveille C, Gormally E, Matullo G, Overvad K, Raaschou-Nielsen O, Clavel-Chapelon F, Linseisen J, Boeing H, Trichopoulou A, Trichopoulos D, Kaladidi A, Palli D, Krogh V, Tumino R, Panico S, Bueno-De-Mesquita HB, Peeters PH, Kumle M, Gonzalez CA, Martinez C, Dorronsoro M, Barricarte A, Navarro C, Quiros JR, Berglund G, Janzon L, Jarvholm B, Day NE, Key TJ, Saracci R, Kaaks R, Riboli E, and Vineis P. 2005. DNA adducts and lung cancer risk: a prospective study. *Cancer Res* 65:8042–8.
- Pereyra-Munoz N, Rugerio-Vargas C, Angoa-Perez M, Borgonio-Perez G, and Rivas-Arancibia S. 2006. Oxidative damage in substantia nigra and striatum of rats chronically exposed to ozone. *J Chem Neuroanat* 31:114–23.
- Plopper CG, Hatch GE, Wong V, Duan X, Weir A J, Tarkington BK, Devlin RB, Becker S, and Buckpitt AR. 1998. Relationship of inhaled ozone concentration to acute tracheobronchial epithelial injury, site-specific ozone dose and glutathione depletion in rhesus monkeys. *Am J Respir Cell Mol Biol* 19:387–99.
- Polosa R, Sapsford RJ, Dokic D, Cacciola RR, Prosperini G, Devalia JL, Holgate ST, Howarth PH, and Davies DE. 2004. Induction of the epidermal growth factor receptor and its ligands in nasal epithelium by ozone. *J Allergy Clin Immunol* 113:120–6.
- Pope CA III, Burnett RT, Thun MJ, Calle EE, Krewski D, Ito K, and Thurston GD. 2002. Lung cancer, cardiopulmonary mortality, and long-term exposure to fine particulate air pollution. *JAMA* 287:1132–1141.
- Poupard O, Blondeau P, Iordache V, and Allard F. 2005. Statistical analysis of parameters influencing the relationship between outdoor and indoor air quality in schools. *Atmos Env* 39:2071–80.
- Pryor WA. 1992. How far does ozone penetrate into the pulmonary air/tissue boundary before it reacts? *Free Radic Biol Med* 12:83–8.
- Pulfer MK and Murphy RC. 2004. Formation of biologically active oxysterols during ozonolysis of cholesterol present in lung surfactant. *J Biol Chem* 279:26331–8.
- Pulfer MK, Taube C, Gelfand E, and Murphy RC. 2005. Ozone exposure *in vivo* and formation of biologically active oxysterols in the lung. *J Pharmacol Exp Ther* 312:256–64.

- Rabinovitch N, Zhang L, Murphy JR, Vedal S, Dutton SJ, and Gelfand EW. 2004. Effects of wintertime ambient air pollutants on asthma exacerbations in urban minority children with moderate to severe disease. *J Allergy Clin Immunol* 114:1131–7.
- Rainham DG, Smoyer-Tomic KE, Sheridan SC, and Burnett RT. 2005. Synoptic weather patterns and modification of the association between air pollution and human mortality. *Int J Environ Health Res* 15:347–60.
- Ratto J, Wong H, Liu J, Fahy J, Boushey H, Solomon C, and Balmes J. 2006. Effects of multiday exposure to ozone on airway inflammation as determined using sputum induction. *Environ Health Perspect* 114:209–12.
- Reeser WH, Lee GM, Taylor A, Wang L, Arnold SF, Ultman JS, and Ben-Jebria A. 2005. Uptake of ozone in human lungs and its relationship to local physiological response. *Inhal Toxicol* 17:699–707.
- Reiss R, Ryan PB, Tibbetts SJ, and Koutrakis P. 1995. Measurement of organic acids, aldehydes, and ketones in residential environments and their relation to ozone. *J Air Waste Man Assoc* 45:811–22.
- Ren YH, Qin XQ, Guan CX, Luo ZQ, Zhang CQ, and Sun XH. 2004. Temporal and spatial distribution of VIP, CGRP and their receptors in the development of airway hyperresponsiveness in the lungs. *Sheng Li Xue Bao* 56:137–46.
- Rich DQ, Mittleman MA, Link MS, Schwartz J, Luttmann-Gibson H, Catalano PJ, Speizer FE, Gold DR, and Dockery DW. 2006a. Increased risk of paroxysmal atrial fibrillation episodes associated with acute increases in ambient air pollution. *Environ Health Perspect* 114:120–3.
- Rich DQ, Kim MH, Turner JR, Mittleman MA, Schwartz J, Catalano PJ, and Dockery DW. 2006b. Association of ventricular arrhythmias detected by implantable cardioverter defibrillator and ambient air pollutants in the St Louis, Missouri metropolitan area. *Occup Environ Med* 63:591–6.
- Riediker M, Williams R, Devlin R, Griggs T, and Bromberg P. 2003. Exposure to particulate matter, volatile organic compounds, and other air pollutants inside patrol cars. *Environ Sci Technol* 37:2084–93.
- Rigas ML, Ben-Jebria A, and Ultman JS. 1997. Longitudinal distribution of ozone absorption in the lung: effects of nitrogen dioxide, sulfur dioxide, and ozone exposures. *Arch Environ Health* 52:173–8.
- Rigas ML, Catlin SN, Ben-Jebria A, and Ultman JS. 2000. Ozone uptake in the intact human respiratory tract: relationship between inhaled dose and actual dose. *J Appl Physiol* 88:2015–22.
- Ritz B, Wilhelm M, and Zhao Y. 2006. Air pollution and infant death in southern California, 1989–2000. *Pediatrics* 118:493–502.
- Rivera-Sanchez YM, Johnston RA, Schwartzman IN, Valone J, Silverman ES, Fredberg JJ, and Shore SA. 2004. Differential effects of ozone on airway and tissue mechanics in obese mice. *J Appl Physiol* 96:2200–6.
- Romero-Velazquez RM, Alfaro-Rodriguez A, Gonzalez-Pina R, and Gonzalez-Maciél A. 2002. Effect of ozone prenatal exposure on postnatal development of cerebellum. *Proc West Pharmacol Soc* 45:65–7.

- Romieu I, Ramirez-Aguilar M, Sienna-Monge JJ, Moreno-Macias H, del Rio-Navarro BE, David G, Marzec J, Hernandez-Avila M, and London S. 2006. GSTM1 and GSTP1 and respiratory health in asthmatic children exposed to ozone. *Eur Respir J* 28:953-9.
- Rubio C and Paz C. 2003. Indomethacin reverts sleep disorders produced by ozone exposure in rats. *Toxicology* 191:89–96.
- Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, and Gilliland FD. 2005. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. *Environ Health Perspect* 113:1638–44.
- Sanchez-Gonzalez DJ, Moro MA, Castillo-Henkel C, Herrera-Gonzalez N, Hernandez-Pando R, Larios-Medina FJ, Cobilt R, Blanco JA, Pedraza-Chaverri J, and Villanueva C. 2004. Ozone exposure induces iNOS expression and tyrosine nitration in rat aorta. *Environmental Toxicology and Pharmacology* 17:1–7.
- Santiago L Y, Hann MC, Ben-Jebria A, and Ultman JS. 2001. Ozone absorption in the human nose during unidirectional airflow. *J Appl Physiol* 91:725–32.
- Santucci D, Sorace A, Francia N, Aloe L, and Alleva E. 2006. Prolonged prenatal exposure to low-level ozone affects aggressive behaviour as well as NGF and BDNF levels in the central nervous system of CD-1 mice. *Behav Brain Res* 166:124–30.
- Sarangapani R, Gentry PR, Covington TR, Teeguarden JG, and Clewell HJ III. 2003. Evaluation of the potential impact of age- and gender-specific lung morphology and ventilation rate on the dosimetry of vapors. *Inhalation Toxicol* 15:987–1016.
- Sarnat JA, Koutrakis P, and Suh HH. 2000. Assessing the relationship between personal particulate and gaseous exposures of senior citizens living in Baltimore, MD. *J Air Waste Man Assoc* 50:1184–98.
- Sarnat JA, Brown KW, Schwartz J, Coull BA, and Koutrakis P. 2005. Ambient gas concentrations and personal particulate matter exposures: implications for studying the health effects of particles. *Epidemiology* 16:385–95.
- Sarnat SE, Suh HH, Coull BA, Schwartz J, Stone PH, and Gold DR. 2006a. Ambient particulate air pollution and cardiac arrhythmia in a panel of older adults in Steubenville, Ohio. *Occup Environ Med* 63:700–6.
- Schierhorn K, Hanf G, Fischer A, Umland B, Olze H, and Kunkel G. 2002. Ozone-induced release of neuropeptides from human nasal mucosa cells. *Int Arch Allergy Immunol* 129:145–51.
- Schildcrout JS, Sheppard L, Lumley T, Slaughter JC, Koenig JQ, and Shapiro GG. 2006. Ambient air pollution and asthma exacerbations in children: an eight-city analysis. *Am J Epidemiol* 164:505–17.
- Schmelzer KR, Wheelock AM, Dettmer K, Morin D, and Hammock BD. 2006. The role of inflammatory mediators in the synergistic toxicity of ozone and 1-nitronaphthalene in rat airways. *Environ Health Perspect* 114:1354–60.
- Servais S, Boussouar A, Molnar A, Douki T, Pequignot JM, and Favier R. 2005. Age-related sensitivity to lung oxidative stress during ozone exposure. *Free Radic Res* 39:305–16.
- Simpson R, Williams G, Petroschevsky A, Best T, Morgan G, Denison L, Hinwood A, Neville G, and Neller A. 2005a. The short-term effects of air pollution on daily mortality in four Australian cities. *Aust N Z J Public Health* 29:205–12.

- Simpson R, Williams G, Petroeschevsky A, Best T, Morgan G, Denison L, Hinwood A, and Neville G. 2005b. The short-term effects of air pollution on hospital admissions in four Australian cities. *Aust N Z J Public Health* 29:213–21.
- Sokol RZ, Kraft P, Fowler IM, Mamet R, Kim E, and Berhane KT. 2006. Exposure to environmental ozone alters semen quality. *Environ Health Perspect* 114:360–5.
- Soulage C, Perrin D, Cottet-Emard JM, Pequignot J, Dalmaz Y, and Pequignot JM. 2004. Central and peripheral changes in catecholamine biosynthesis and turnover in rats after a short period of ozone exposure. *Neurochem Int* 45:979–86.
- Steck-Scott S, Arab L, Craft NE, and Samet JM. 2004. Plasma and lung macrophage responsiveness to carotenoid supplementation and ozone exposure in humans. *Eur J Clin Nutr* 58:1571–9.
- Steerenberg PA, Bischoff EW, de Klerk A, Verlaan AP, Jongbloets LM, van Loveren H, Opperhuizen A, Zomer G, Heisterkamp SH, Hady M, Spieksma FT, Fischer PH, Dormans JA, and van Amsterdam JG. 2003. Acute effect of air pollution on respiratory complaints, exhaled NO and biomarkers in nasal lavages of allergic children during the pollen season. *Int Arch Allergy Immunol* 131:127–37.
- Stieb DM, Smith-Doiron M, Brook JR, Burnett RT, Dann T, Mamedov A, and Chen Y. 2002. Air pollution and disability days in Toronto: results from the national population health survey. *Environ Res* 89:210–19.
- Takeuchi C, Galve R, Nieva J, Witter DP, Wentworth AD, Troseth RP, Lerner RA, and Wentworth P Jr. 2006. Proatherogenic effects of the cholesterol ozonolysis products, atheronal-A and atheronal-B. *Biochemistry* 45:7162–70.
- Taylor AB, Lee GM, Nellore K, Ben-Jebria A, and Ultman JS. 2006. Changes in the carbon dioxide expirogram in response to ozone exposure. *Toxicol Appl Pharmacol* 213:1–9.
- Thomson E, Kumarathasan P, Goegan P, Aubin RA, and Vincent R. 2005. Differential regulation of the lung endothelin system by urban particulate matter and ozone. *Toxicol Sci* 88:103–13.
- Thomson E, Kumarathasan P, and Vincent R. 2006. Pulmonary expression of preproET-1 and preproET-3 mRNAs is altered reciprocally in rats after inhalation of air pollutants. *Exp Biol Med* 231:979–84.
- Timonen KL, Hoek G, Heinrich J, Bernard A, Brunekreef B, de Hartog J, Hameri K, Ibaldo-Mulli A, Mirme A, Peters A, Tiittanen P, Kreyling WG, and Pekkanen J. 2004. Daily variation in fine and ultrafine particulate air pollution and urinary concentrations of lung Clara cell protein CC16. *Occup Environ Med* 61:908–14.
- Timonen KL, Vanninen E, de Hartog J, Ibaldo-Mulli A, Brunekreef B, Gold DR, Heinrich J, Hoek G, Lanki T, Peters A, Tarkiainen T, Tiittanen P, Kreyling W, and Pekkanen J. 2006. Effects of ultrafine and fine particulate and gaseous air pollution on cardiac autonomic control in subjects with coronary artery disease: The ULTRA study. *J Expo Sci Environ Epidemiol* 16:332–41.
- Tobias A, Saez M, Galan I, and Campbell MJ. 2003. Sensitivity analysis of common statistical models used to study the short-term effects of air pollution on health. *Int J Biometeorol* 47:227–9.
- Tovalin H, Valverde M, Morandi MT, Blanco S, Whitehead L, and Rojas E. 2006. DNA damage in outdoor workers occupationally exposed to environmental air pollutants. *Occup Environ Med* 63:230–6.

Toward TJ and Broadley KJ. 2002. Airway function, oedema, cell infiltration and nitric oxide generation in conscious ozone-exposed guinea-pigs: effects of dexamethasone and rolipram. *Br J Pharmacol* 136:735–45.

Triche EW, Gent JF, Holford TR, Belanger K, Bracken MB, Beckett WS, Naeher L, McSharry JE, and Leaderer BP. 2006. Low-level ozone exposure and respiratory symptoms in infants. *Environ Health Perspect* 114:911–6.

Ultman J S, Ben-Jebria A, and Arnold SF. 2004. Uptake distribution of ozone in human lungs: intersubject variability in physiologic response. *Res Rep Health Eff Inst* 125:1–23; discussion 25–30.

Urch B, Brook JR, Wasserstein D, Brook RD, Rajagopalan S, Corey P, and Silverman F. 2004. Relative contributions of PM_{2.5} chemical constituents to acute arterial vasoconstriction in humans. *Inhal Toxicol* 16:345–52.

Urch B, Silverman F, Corey P, Brook JR, Lukic KZ, Rajagopalan S, and Brook RD. 2005. Acute blood pressure responses in healthy adults during controlled air pollution exposures. *Environ Health Perspect* 113:1052–55.

US Environmental Protection Agency. 1996. 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 online at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923&CFID=1963237&CFTOKEN=60787687&jsessionid=2030e70d4661fa428b2927a1123e7a3fa573TR4a3020302e302830>

US Environmental Protection Agency. 2004. Air Quality Criteria for Particulate Matter. Washington, DC. Publication No. EPA 600/R-05/004aF.

US Environmental Protection Agency. 2006. Air Quality Criteria for Ozone and Related Photochemical Oxidants. Washington, DC: Publication No. EPA 600/R-05/004aF-cF 3v. Available online at: <http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=149923&CFID=1963237&CFTOKEN=60787687&jsessionid=2030e70d4661fa428b2927a1123e7a3fa573TR4a3020302e302830>

Valacchi G, Pagnin E, Corbacho AM, Olano E, Davis PA, Packer L, and Cross CE. 2004. *In vivo* ozone exposure induces antioxidant/stress-related responses in murine lung and skin. *Free Radic Biol Med* 36:673–81.

Villeneuve PJ, Chen L, Stieb D, and Rowe, BH. 2006a. Associations between outdoor air pollution and emergency department visits for stroke in Edmonton, Canada. *Euro J Epidemiol* 21:689–700.

Villeneuve PJ, Doiron MS, Stieb D, Dales R, Burnett RT, and Dugandzic R. 2006b. Is outdoor air pollution associated with physician visits for allergic rhinitis among the elderly in Toronto, Canada? *Allergy* 61:750–8.

von Klot S, Peters A, Aalto P, Bellander T, Berglind N, D'Ippoliti D, Elosua R, Hormann A, Kulmala M, Lanki T, Lowel H, Pekkanen J, Picciotto S, Sunyer J, and Forastiere F. 2005. Ambient air pollution is associated with increased risk of hospital cardiac readmissions of myocardial infarction survivors in five European cities. *Circulation* 112:3073–9.

Wade KS, Mulholland JA, Marmur A, Russell AG, Hartsell B, Edgerton E, Klein M, Waller L, Peel JL, and Tolbert PE. 2006. Effects of instrument precision and spatial variability on the assessment of the temporal variation of ambient air pollution in Atlanta, Georgia. *J Air Waste Man Assoc* 56:876–88.

- Wang G, Bates-Kenney SR, Tao JQ, Phelps DS, and Floros J. 2004. Differences in biochemical properties and in biological function between human SP-A1 and SP-A2 variants, and the impact of ozone-induced oxidation. *Biochemistry* 43:4227–39.
- Wang J, Wang S, Manzer R, McConville G, and Mason RJ. 2006. Ozone induces oxidative stress in rat alveolar type II and type I-like cells. *Free Radic Biol Med* 40:1914–28.
- Weschler CJ, Shields HC, and Naik DV. 1994. Indoor chemistry involving O₃, NO, and NO₂ as evidenced by 14 months of measurements at a site in Southern California. *Environ Sci Technol* 28:2120–32.
- Wheelock AM, Boland BC, Isbell M, Morin D, Wegesser TC, Plopper CG, and Buckpitt AR. 2005. *In vivo* effects of ozone exposure on protein adduct formation by 1-nitronaphthalene in rat lung. *Am J Respir Cell Mol Biol* 33:130–7.
- Wilhelm M and Ritz B. 2003. Residential proximity to traffic and adverse birth outcomes in Los Angeles County, California, 1994–1996. *Environ Health Perspect* 111:207–16.
- Wilhelm M and Ritz B. 2005. Local variations in CO and particulate air pollution and adverse birth outcomes in Los Angeles County, California, USA. *Environ Health Perspect* 113:1212–21.
- Wilkins CK, Wolkoff P, Clausen PA, Hammer M, and Nielsen GD. 2003. Upper airway irritation of terpene/ozone oxidation products (TOPS). Dependence on reaction time, relative humidity and initial ozone concentration. *Toxicol Lett* 143:109–14.
- Wong TW, Tam WS, Yu TS, and Wong AH. 2002. Associations between daily mortalities from respiratory and cardiovascular diseases and air pollution in Hong Kong, China. *Occup Environ Med* 59:30–5.
- World Health Organization. 2003. Health Aspects of Air Pollution with Particulate Matter, Ozone and Nitrogen Dioxide. Report on a WHO Working Group, Bonn, Germany, 13–15 January 2003. Publication No. E79097.
- Wu ZX, Satterfield BE, and Dey RD. 2003. Substance P released from intrinsic airway neurons contributes to ozone-enhanced airway hyperresponsiveness in ferret trachea. *J Appl Physiol* 95:742–50.
- Xue J, Liu SV, Ozkaynak H, and Spengler JD. 2005. Parameter evaluation and model validation of ozone exposure assessment using Harvard Southern California Chronic Ozone Exposure Study data. *J Air Waste Man Assoc* 55:1508–15.
- Yoshida M, Aizawa H, Inoue H, Koto H, Nakano H, Komori M, Fukuyama S, and Hara N. 2002. Ozone exposure may enhance airway smooth muscle contraction by increasing Ca(2+) refilling of sarcoplasmic reticulum in guinea pig. *Pulm Pharmacol Ther* 15:111–19.
- Yost BL, Gleich GJ, Jacoby DB, and Fryer AD. 2005. The changing role of eosinophils in long-term hyperreactivity following a single ozone exposure. *Am J Physiol Lung Cell Mol Physiol* 289:L627–35.
- Zanobetti A, Canner MJ, Stone PH, Schwartz J, Sher D, Eagan-Bengston E, Gates KA, Hartley LH, Suh H, and Gold DR. 2004. Ambient pollution and blood pressure in cardiac rehabilitation patients. *Circulation* 110:2184–9.
- Zeghnoun A, Czernichow P, and Declercq C. 2003. Assessment of short-term association between health outcomes and ozone concentrations using a Markov regression model. *Environmetrics* 14:271–82.