United States
Environmental Protection
Agency

Office of Research and
Development
Washington DC 20460

EPA/600/P-95/001cF
April 1996

EPA

Air Quality Criteria for Particulate Matter

Volume III of III

DISCLAIMER

This document has been reviewed in accordance with U.S. Environmental Protection Agency policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

PREFACE

On April 30, 1971 (Federal Register, 1971), in accordance with the Clean Air Act (CAA) Amendments of 1970, the U.S. Environmental Protection Agency (EPA) promulgated the original primary and secondary National Ambient Air Quality Standard (NAAQS) for particulate matter (PM). The reference method for measuring attainment of these standards was the "high-volume" sampler (Code of Federal Regulations, 1977), which collected PM up to a nominal size of 25 to 45 μm (so-called "total suspended particulate," or "TSP"). Thus, TSP was the original indicator for the PM standards. The primary standards for PM, measured as TSP, were 260 $\mu g/m^3$, 24-h average not to be exceeded more than once per year, and 75 $\mu g/m^3$, annual geometric mean. The secondary standard was 150 $\mu g/m^3$, 24-h average not to be exceeded more than once per year.

In accordance with the CAA Amendments of 1977, the U.S. EPA conducted a re-evaluation of the scientific data for PM, resulting in publication of a revised air quality criteria document (AQCD) for PM in December 1982 and a later Addendum to that document in 1986. On July 1, 1987, the U.S. EPA published final revisions to the NAAQS for PM. The principle revisions to the 1971 NAAQS included (1) replacing TSP as the indicator for the ambient standards with a new indicator that includes particles with an aerodynamic diameter less than or equal to a nominal 10 μm ("PM_{10}"), (2) replacing the 24-h primary TSP standard with a 24-h PM_{10} standard of 150 $\mu g/m^3$, (3) replacing the annual primary TSP standard with an annual PM_{10} standard of 50 $\mu g/m^3$, and (4) replacing the secondary TSP standard with 24-h and annual PM_{10} standards identical in all respects to the primary standards.

The present PM AQCD has been prepared in accordance with the CAA, requiring the EPA Administrator periodically to review and revise, as appropriate, the criteria and NAAQS for listed criteria pollutants. Emphasis has been place on the presentation and evaluation of the latest available dosimetric and health effects data; however, other scientific data are also presented to provide information on the nature, sources, size distribution, measurement, and concentrations of PM in the environment and contributions of ambient PM to total human exposure. This document is comprised of three volumes, with the present one (Volume III) containing Chapters 12 through 13.

This document was prepared by U.S. EPA's National Center for Environmental Assessment-RTP, with assistance by scientists from other EPA Office of Research and Development laboratories (NERL; NHEERL) and non-EPA expert consultants. Several earlier drafts of the document were reviewed by experts from academia, various U.S. Federal and State government units, non-governmental health and environmental organizations, and private industry. Several versions of this AQCD have also been reviewed in public meetings by the Agency's Clean Air Scientific Advisory Committee (CASAC). The National Center for Environmental Assessment (formerly the Environmental Criteria and Assessment Office) of the U.S. EPA's Office of Research and Development acknowledges with appreciation the valuable contributions made by the many authors, contributors, and reviewers, as well as the diligence of its staff and contractors in the preparation of this document.

Air Quality Criteria for Particulate Matter

TABLE OF CONTENTS

Volume I

Volume II

TABLE OF CONTENTS (cont'd)

Volume III

TABLE OF CONTENTS

TABLE OF CONTENTS (cont'd)

TABLE OF CONTENTS (cont'd)

TABLE OF CONTENTS (cont'd)

LIST OF TABLES

LIST OF TABLES (cont'd)

LIST OF TABLES (cont'd)

LIST OF FIGURES

LIST OF FIGURES (cont'd)

LIST OF FIGURES (cont'd)

LIST OF FIGURES (cont'd)

AUTHORS, CONTRIBUTORS, AND REVIEWERS

CHAPTER 12. EPIDEMIOLOGY STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO AIRBORNE PARTICLES/ACID AEROSOLS

Principal Authors

Dr. Robert Chapman—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lester D. Grant—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Office, Research Triangle Park, NC 27711

Dr. Vic Hasselblad—29 Autumn Woods Drive, Durham, NC 27713

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

Dr. Laurence Kalkstein—University of Delaware, Center of Climatic Research, Newark, DE 19716-2541

Dr. Dennis Kotchmar—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Frederick Lipfert—23 Carll Court, Northport, NY 11768

Dr. Allan Marcus—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

Contributors and Reviewers

Dr. Philip Bromberg—University of North Carolina, School of Medicine, Chapel Hill, NC 27599-0126

Dr. Bert Brunekreef—The University of Wageningen, Department of Epidemiology and Public Health, P.O. Box 238, 6700 A E Wageningen, The Netherlands

Dr. Richard Burnett—Health and Welfare Canada, 203 Environmental Health Center, Tunney's Pasture, Ottwaw, Ontario, Canada K1A 0L2

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

Contributors and Reviewers (cont'd)

Dr. Douglas Dockery—Harvard School of Public Health, Environmental Epidemiology, 665 Huntington Avenue, Boston, MA 02115

Dr. Klea Katsouyanni—University of Athens, School of Medicine, Department of Hygiene and Epidemiology, 1327 Athens, Greece

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

Dr. Aparna Koppikar—Human Health Assessment Group, U.S. Environmental Protection Agency, (8602), Waterside Mall, 401 M. St. S.W., Washington, DC 20460

Dr. Dennis Kotchmar—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Thomas Louis—University of Minnesota, School of Public Health, A-460 Mayo Building, Box 197, 420 Delaware Street, S.E., Minneapolis, MN 55455

Dr. Joseph Lyon—University of Utah, Department of Family and Preventative Medicine, 50 North Medical Drive, Salt Lake City, UT 84132

Dr. David Mage—National Exposure Research Laboratory (MD-75), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Allan Marcus—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Suresh Moolgavkar—Fred Hutchinson Cancer Research Center, 1124 Columbia Street, Seattle, WA 98104

Dr. William Nelson—National Exposure Research Laboratory (MD-56), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Bart Ostro—California Environmental Protection Agency, 2151 Berkeley Way, Annex 11, Berkeley, CA 94704

Contributors and Reviewers (cont'd)

Dr. C. Arden Pope, III—Brigham Young University, Department of Economics, Provo, Utah 84602

Dr. James Quackenboss—Characterization Research Division, U.S. Environmental Protection Agency, P.O. Box 93478, Las Vegas, NV 89193-3478

Dr. H. Daniel Roth—Roth Associates, 6115 Executive Boulevard, Rockville, MD 20852

Dr. Carl Shy—University of North Carolina, Department of Epidemiology, School of Public Health, Campus Box 7400, Chapel Hill, NC 27599

Dr. Ira B. Tager—University of California-Berkeley, School of Public Health, 140 Warren Hall, Berkeley, CA 94720-7360

Dr. Duncan Thomas—University of Southern California, Preventative Medicine Department, 1420 San Pablo Street, Los Angeles, CA 90033-9987

Dr. Dianne Wagener—National Center for Health Statistics, Mortality Statistics Branch, Division of Vital Statistics, Center for Disease Control, 6526 Belcrest Road, Hyattsville, MD 20782

Dr. Mary C. White—Centers for Disease Control, National Center for Environmental Health, 4770 Buford Highway, NE, Atlanta, GA 30341-3724

Dr. William E. Wilson—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Ronald Wyzga—Electric Power Research Institute, 3420 Hillview Avenue, Palo Alto, CA 94304

CHAPTER 13. INTEGRATIVE SYNTHESIS: KEY POINTS REGARDING PARTICULATE MATTER EXPOSURE, DOSIMETRY, AND HEALTH RISKS

Principal Authors

Dr. Paul Altshuller—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Robert Chapman—National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Principal Authors (cont'd)

Dr. Lawrence J. Folinsbee—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. William Ewald—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jeff Gift—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lester D. Grant—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Annie M. Jarabek—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis Kotchmar—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Allan Marcus—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James McGrath—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph P. Pinto—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. William E. Wilson—National Center for Environmental Assessment (MD-52),
U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Contributors and Reviewers

Dr. Judith A. Graham—National Exposure Research Laboratory (MD-77), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Jeannette Wiltse—Office of Research and Development, U.S. Environmental Protection Agency (8601), Waterside Mall, 401 M St. S.W., Washington, DC 20460

U.S. ENVIRONMENTAL PROTECTION AGENCY
PARTICULATE MATTER MORTALITY WORKSHOP
(NOVEMBER 1994) PARTICIPANTS

Dr. Kenneth Brown—P.O. Box 16608, Chapel Hill, NC 27516-6608

Dr. Douglas Dockery—Harvard School of Public Health, Environmental Epidemiology, 665 Huntington Avenue, Boston, MA 02115

Dr. David Fairley—Bay Area Air Quality Management District, 939 Ellis St., San Francisco, CA 94109

Dr. Lester D. Grant—Director, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

Dr. Laurence Saul Kalkstein—Center for Climatic Research, Department of Geography, University of Delaware, Newark, DE 19716-2541

Dr. Patrick Kinney—Columbia University School of Public Health, Division of Environmental Science, 60 Haven Ave. B-1, New York, NY 10032

Dr. Dennis Kotchmar—Medical Officer, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lisa LaVange—Research Triangle Institute, P.O. Box 12194, Research Triangle Park, NC 27709-2194

Dr. Paul J. Lioy—Environmental Occupational Health Science Institute, 681 Frelinghuysen Lane, Piscataway, NJ 08854

Dr. Frederick Lipfert—23 Carll Court, Northport, NY 11768

Dr. Thomas Louis—University of Minnesota, School of Public Health, A-460 Mayo Building, Box 197, 420 Delaware Street, S.E., Minneapolis, MN 55455

Dr. Allan Marcus—Statistican, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Suresh Moolgavkar—Fred Hutchinson Cancer Reseaarch Center, 1124 Columbia Street, Seattle, WA 98104

Dr. C. Arden Pope, III—Professor of Economics, Brigham Young University, Provo, Utah 84602

Dr. James Quackenboss—Environmental Monitoring Systems Laboratory, U.S. Environmental Protection Agency, P.O. Box 93478, Las Vegas, NV 89193-3478

Dr. H. Daniel Roth—Roth Associates, 6115 Executive Boulevard, Rockville, MD 20852

Dr. Paulo Saldiva—Associate Professor, Department of Pathology, Faculty of Medicine, University of Sao Paulo, Av. Dr. Arnaldo 455, Sao Paulo, SP. CEP 01246-803, BRAZIL

Dr. Jonathan M. Samet—Chairman, Department of Epidemiology, School of Hygiene and Public Health, Johns Hopkins University, 615 N. Wolfe Street, Suite 6039, Baltimore, Maryland 21205-2179

Dr. Joel Schwartz—Environmental Epidemiology Program, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115

Dr. Carl Shy—Professor and Chair, Department of Epidemiology, School of Public Health, Campus Box 7400, University of North Carolina, Chapel Hill, NC 27599

Dr. Claudia M. Spix—BUGH Wuppertal FB A4, FG Arbeitssicherheit und Umweltmedizin (Labor Safety & Environmental Medicine), Gauss Strasse 20 D 42097 Wuppertal, GERMANY

Dr. Patricia Styer—ACBM, The Technological Institute, Northwestern University, 2145 Sheridan Road, Room A130, Evanston, IL 60208-4400

Dr. Jordi Sunyer—Epidemiology Department, School of Hygiene and Public Health, Johns Hopkins University, 624 N. Broadway, Baltimore, MD 21205

Dr. Duncan Thomas—University of Southern California, Preventative Medicine Department, 1420 San Pablo Street, Los Angeles, CA 90033-9987

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

Dr. Diane Wagener—Special Assistant to the Director for Environmental Epidemiology, National Center for Health Statistics, 6525 Belcrest Rd., Room 750, Hyattsville, MD 20782

Dr. William E. Wilson—Technical Consultant, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Ronald Wyzga—Electric Power Research Institute, 3412 Hillview Avenue, Palo Alto, CA 94304

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE

PARTICULATE MATTER CRITERIA DOCUMENT REVIEW

Chairman

Dr. George T. Wolff—General Motors Corporation, Environmental and Energy Staff, General Motors Bldg., 12th Floor, 3044 West Grand Blvd., Detroit, MI 48202

Members

Dr. Stephen Ayres—Office of International Health Programs, Virginia Commonwealth University, Medical College of Virginia, Box 980565, Richmond, VA 23298

Dr. Philip Hopke—Clarkson University, Box 5810, Pottsdam, NY 13699-5810

Dr. Jay Jacobson—Boyce Thompson Institute, Tower Road, Cornell University, Ithaca, NY 14853

Dr. Joseph Mauderly—Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, P.O. Box 5890, Albuquerque, NM 87185

Dr. Paulette Middleton—Science and Policy Associates, 3445 Penrose Place, Suite 140, Boulder, CO 80301

Dr. James H. Price, Jr.—Research and Technology Section, Texas Natural Resources Conservation Commission, P.O. Box 13087, Austin, TX 78711-3087

Invited Scientific Advisory Board Members

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

Dr. Roger O. McClellan—Chemical Industry Institute of Toxicology, P.O. Box 12137, Research Triangle Park, NC 27711

Consultants

Dr. Petros Koutrakis—Harvard School of Public Health, 665 Huntington Avenue, Boston, MA 02115

U.S. ENVIRONMENTAL PROTECTION AGENCY
SCIENCE ADVISORY BOARD
CLEAN AIR SCIENTIFIC ADVISORY COMMITTEE
(cont'd)

Consultants (cont'd)

Dr. Kinley Larntz—Department of Applied Statistics, University of Minnesota, 352 COB, 1994 Buford Avenue, St. Paul, MN 55108-6042

Dr. Allan Legge—Biosphere Solutions, 1601 11th Avenue, N.W., Calgary, Alberta T2N 1H1, Canada

Dr. Daniel Menzel—Department of Community and Environmental Medicine, University of California—Irvine, 19172 Jamboree Boulevard, Irvine, CA 92717-1825

Dr. William R. Pierson—Energy and Environmental Engineering Center, Desert Research Institute, P.O. Box 60220, Reno, NV 89506-0220

Dr. Jonathan Samet—Johns Hopkins University, School of Hygiene and Public Health, Department of Epidemiology, 615 N. Wolfe Street, Baltimore, MD 21205

Dr. Christian Seigneur—Atmospheric and Environmental Research, Inc., 6909 Snake Road, Oakland, CA 94611

Dr. Carl M. Shy—Department of Epidemiology, School of Public Health, University of North Carolina, CB #7400 McGravran-Greenberg Hall, Chapel Hill, NC 27599-7400

Dr. Frank Speizer—Harvard Medical School, Channing Laboratory, 180 Longwood Avenue, Boston, MA 02115

Dr. Jan Stolwijk—Epidemiology and Public Health, Yale University, 60 College Street, New Haven, CT 06510

Dr. Mark J. Utell—Pulmonary Disease Unit, Box 692, University of Rochester Medical Center, 601 Elmwood Avenue, Rochester, NY 14642

Dr. Warren White—Washington University, Campus Box 1134, One Brookings Drive, St. Louis, MO 63130-4899

Designated Federal Official

Mr. Randall C. Bond—Science Advisory Board (1400), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460

Mr. A. Robert Flaak—Science Advisory Board (1400), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460

Staff Assistant

Ms. Janice M. Cuevas—Science Advisory Board (1400), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460

Secretary

Ms. Lori Anne Gross—Science Advisory Board (1400), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460

Ms. Connie Valentine—Science Advisory Board (1400), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, DC 20460

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

Scientific Staff

Dr. Lester D. Grant—Director, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Michael A. Berry—Deputy Director, National Center for Environmental Assessment, (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Dennis Kotchmar—Project Manager, Medical Officer, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beverly Comfort—Deputy Project Manager/Technical Project Officer, Health Scientist, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Lawrence J. Folinsbee—Chief, Environmental Media Assessment Group, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. A. Paul Altshuller—Technical Consultant, Senior Atmospheric Scientist, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 (Retired)

Dr. Robert Chapman—Technical Consultant, Medical Officer, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. William Ewald—Technical Project Officer, Health Scientist, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Norman Childs—Chief, Environmental Media Assessment Branch, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 (Retired)

Dr. Judith A. Graham—Associate Director for Health, National Exposure Research Laboratory (MD-77), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

Scientific Staff (cont'd)

Ms. Annie M. Jarabek—Technical Project Officer, Toxicologist, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Allan Marcus—Technical Project Officer, Statistician, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. James McGrath—Technical Project Officer, Visiting Senior Health Scientist, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Dr. Joseph P. Pinto—Technical Project Officer, Physical Scientist, National Center for Environmental Assessment, U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Beverly Tilton—Technical Project Officer, Physical Scientist, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711 (Retired)

Dr. William E. Wilson—Technical Consultant, Physical Scientist, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Technical Support Staff

Mr. Douglas B. Fennell—Technical Information Specialist, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Emily R. Lee—Management Analyst, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Diane H. Ray—Program Analyst, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

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

Technical Support Staff (cont'd)

Ms. Eleanor Speh—Office Manager, Environmental Media Assessment Branch, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Ms. Donna Wicker—Administrative Officer, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Mr. Richard Wilson—Clerk, National Center for Environmental Assessment (MD-52), U.S. Environmental Protection Agency, Research Triangle Park, NC 27711

Document Production Staff

Ms. Marianne Barrier—Graphic Artist, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Mr. John R. Barton—Document Production Coordinator, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Mr. Donald L. Duke—Project Director, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Ms. Shelia H. Elliott—Word Processor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Ms. Sandra K. Eltz—Word Processor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Ms. Sheila R. Lassiter—Word Processor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Ms. Wendy B. Lloyd—Word Processor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Ms. Carolyn T. Perry—Word Processor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Ms. Terri D. Ragan—Personal Computer Technician, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

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

Document Production Staff (cont'd)

Mr. Derrick Stout—Local Area Network System Administrator, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Ms. Cheryl B. Thomas—Word Processor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Technical Reference Staff

Ms. Ginny M. Belcher—Bibliographic Editor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Mr. Robert D. Belton—Bibliographic Editor, Information Organizers, Inc., P.O. Box 14391, Research Triangle Park, NC 27709

Mr. John A. Bennett—Bibliographic Editor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

Ms. S. Blythe Hatcher—Bibliographic Editor, Information Organizers, Inc., P.O. Box 14391, Research Triangle Park, NC 27709

Ms. Susan L. McDonald—Bibliographic Editor, Information Organizers, Inc., P.O. Box 14391, Research Triangle Park, NC 27709

Ms. Deborah L. Staves—Bibliographic Editor, Information Organizers, Inc., P.O. Box 14391, Research Triangle Park, NC 27709

Ms. Patricia R. Tierney—Bibliographic Editor, ManTech Environmental Technology, Inc., P.O. Box 12313, Research Triangle Park, NC 27709

12. EPIDEMIOLOGY STUDIES OF HEALTH EFFECTS ASSOCIATED WITH EXPOSURE TO AIRBORNE PARTICLES/ACID AEROSOLS

12.1 INTRODUCTION

A rapidly growing body of epidemiologic data examines relationships between particulate matter (PM) concentrations and human health effects, ranging from respiratory function changes and symptoms to exacerbation of respiratory disease and excess mortality associated with premature death.

The purpose of this chapter is to review the epidemiological evidence relating health effects to exposure to airborne particles. Much new information has appeared since EPA's publication of the 1982 document on Air Quality Criteria for Particulate Matter and Sulfur Oxides (U.S. Environmental Protection Agency, 1982a), its second Addendum (U.S. Environmental Protection Agency, 1986a), and a later Acid Aerosol Issue Paper (U.S. Environmental Protection Agency, 1989). Information from these previous documents is only concisely considered here to provide background for this chapter and to help form the basis for evaluation of more recent publications.

12.1.1 Definition of Particulate Matter and Measurement Methods

As discussed in Chapter 3, "particulate matter" is the generic term for a broad class of chemically and physically diverse substances that exist as discrete particles (liquid droplets or solids) over a wide range of sizes. Particles originate from a variety of stationary and mobile sources and may be emitted directly or formed in the atmosphere by transformation of gaseous emissions such as sulfur oxides (SO_x), nitrogen oxides NO_x), and volatile organic compounds (VOCs). The chemical and physical properties of PM vary greatly with time, region, meteorology, and source category, thus complicating the assessment of health and welfare effects. Particles in ambient air usually occur in two somewhat overlapping bimodal size distributions: (1) fine (diameter less than 2.5 μm) and (2) coarse (diameter larger than 2.5 μm). The two size fractions tend to have different origins and composition, as discussed in Chapter 3 along with other aspects concerning particle size and atmospheric chemistry.

On July 1, 1987 (Federal Register, 1987), EPA published revisions to the PM NAAQS. The principal revisions in 1987 included replacing TSP as the indicator for the ambient standards with a new indicator that includes only particles with an aerodynamic diameter less than or equal to a nominal 10 μm (PM_{10}).

The choice if PM_{10} as an indicator for the revised standards was based on several key conclusions as summarized below:

(1) Health risks posed by inhaled particles are influenced by both the penetration and deposition of particles in the various regions of the respiratory tract and the biological responses to these deposited materials. Smaller particles penetrate furthest in the respiratory tract. The largest particles are deposited predominantly in the extrathoracic (head) region, with somewhat smaller particles depositing in the tracheobronchial region; still smaller particles can reach the deepest portion of the lung, the pulmonary or alveolar region.

(2) The risks of adverse health effects associated with deposition of typical ambient fine and coarse particles in the thoracic region (tracheobronchial and alveolar deposition) are markedly greater than those associated with deposition in the extrathoracic region. Maximum particle penetration to the thoracic region occurs during oronasal or mouth breathing.

(3) The size-specific indicator for primary standards should represent those particles small enough to penetrate to the thoracic region. The risks of adverse health effects from extrathoracic deposition of typical ambient PM are sufficiently low that particles depositing only in that region can safely be excluded from the indicator.

A variety of PM sampling and measurement methodologies have been used in the epidemiology studies discussed in this chapter. Some studies used earlier measures such as British Smoke (BS), Coefficient of Haze (COHs) and Total Suspended Particulate Matter (TSP). Limitations posed for interpreting epidemiologic studies employing such PM measurement methods are discussed both in U.S. Environmental Protection Agency (1982a, 1986a) and Chapter 4 of this document. Additionally, current measures (i.e., $PM_{2.5}$, PM_{10} and sulfates) used in more recent epidemiology studies are defined and discussed earlier in this document in Chapter 4 (Sampling and Analysis of Particulate Matter). Methodologies for strong acid measurement are also discussed in U.S. Environmental Protection Agency (1989) and in Chapter 4 of this document.

12.1.2 Guidelines for Assessment of Epidemiologic Studies

An important concept of the epidemiologic information assessed here concerns its usefulness in demonstrating cause-effect relationships versus merely establishing associations (which may be non-causal in nature) between PM exposures and various health effects. The interpretation of epidemiologic data as an aid to inferring causal relationships between presumed causal agents and associated effects has been previously discussed by several expert committees or deliberative bodies faced with evaluation of controversial biomedical issues (U.S. Department of Health, Education, and Welfare, 1964; U.S. Senate, 1968). Criteria selected by each for determination of causality included: (1) magnitude of the association; (2) consistency of the association, as evidenced by its repeated observation by different investigators, in different places, circumstances and time; (3) specificity of the association; (4) temporal relationship of the association; (5) coherence of the association in being consistent with other known facts; (6) existence of a biological gradient, for the association; and (7) biological plausibility of the association.

Hill (1965) further noted that strong support for likely causality suggested by an epidemiologic association can be derived from experimental or semi-experimental evidence, where manipulation of the presumed causative agent (its presence or absence, variability in intensity, etc.) also affects the frequency or intensity of the associated effects. Importantly, both Hill (1965) and the above-noted deliberative bodies or expert committees were careful to emphasize that, regardless of the specific set of criteria selected by each, that no one criterion is definitive by itself nor is it necessary that all (except temporal relationship) be fulfilled in order to support a determination of causality. Also, Hill (1965) and several of the expert groups noted that statistical methods alone cannot establish proof of a causal relationship in an association nor does lack of "statistical significance" of an association according to arbitrarily selected probability criteria necessarily negate the possibility of a causal relationship. That is, as stated by the U.S. Surgeon General's Advisory Committee on Smoking and Health (U.S. Department of Health Education and Welfare, 1964): "The causal significance of an association is a matter of judgment which goes beyond any statement of statistical probability." Apropos to this, Bates (1992) has more recently emphasized the importance of assessing the overall coherence of epidemiologic findings of both morbidity and mortality effects at varying pollutant concentrations in making judgements about likely causal relationships.

Taking into account the above, the following types of questions were considered in assessing the relative scientific quality of epidemiologic studies reviewed here and to assist in the interpretations of their findings.

(1) Was the quality of the aerometric data used sufficient to allow for meaningful characterization of geographic or temporal differences in study population pollutant exposures in the range(s) of pollutant concentrations evaluated?

(2) Were the study populations well defined and adequately selected so as to allow for meaningful comparisons between study groups or meaningful temporal analyses of health effects results?

(3) Were the health endpoint measurements meaningful and reliable, including clear definition of diagnostic criteria utilized and consistency in obtaining dependent variable measurements?

(4) Were the statistical analyses used appropriate and properly performed and interpreted, including accurate data handling and transfer during analyses?

(5) Were likely important confounding or covarying factors adequately controlled for or taken into account in the study design and statistical analyses?

(6) Were the reported findings internally consistent, biologically plausible, and coherent in terms of consistency with other known facts?

Few, if any, epidemiologic studies deal with all of the above points in a completely ideal fashion. Nevertheless, these guidelines provide benchmarks for judging the relative quality of various studies and for selecting the best for use in criteria development. Detailed critical analysis of all epidemiologic studies on PM health effects, especially in relation to all of the above questions, is beyond the scope of this document. Of most importance for present purposes are those studies which provide useful qualitative or quantitative information on exposure-effect or exposure-response relationships for health effects associated with ambient air levels of PM currently likely to be encountered in the United States.

Extensive epidemiologic literature on the effects of occupational exposures to various PM specific components is not reviewed here for several reasons:

(1) Such literature generally deals with effects of exposures to PM chemical species at levels many times higher than those encountered in the ambient air by the general population.

(2) Populations exposed occupationally mainly include healthy adults, self-selected to some extent in terms of being better able to tolerate exposures to PM substances than

more susceptible workers seeking alternative employment or other groups often at special risk among the general public (e.g., the old, the chronically ill, young children, and asthmatics).

(3) Extrapolation of observed occupational exposure-health effects relationships (or lack thereof) to the general public (especially population groups at special risk) could, therefore, be potentially misleading in terms of demonstrating health effects among healthy workers at higher exposure levels than would affect susceptible groups in the general population.

The occupational literature does, however, demonstrate links between acute high level or chronic lower level exposures to many different PM chemical species and a variety of health effects, including: pulmonary function changes; respiratory tract diseases; morphological damage to the respiratory system; and respiratory tract cancers. Some consideration of such literature is provided in Chapter 11 on the toxicology of specific PM constituents as useful to elucidate important points on observed exposure-effect relationships.

12.1.3 Epidemiologic Designs and Strategies

The recent epidemiology studies to be discussed generally fall into four categories:

(1) short-term exposure studies related to acute effects, typically on a time scale of one or a few days;

(2) prospective cohort studies, in which health outcomes for individuals recruited at the same time are followed over a period of time, typically several years;

(3) cross-sectional epidemiology studies comparing at a single point in time the health effects of long term-exposures to air pollution of different populations, typically assuming that exposure has occurred over a time interval of several years;

(4) metaanalyses and other syntheses of research studies.

Different types of studies have differing strengths and weaknesses. One limitation common to all of the above different study designs is that only community-level air pollution information is available, generally from one or a few air monitoring stations used to characterize PM and other air pollution and weather exposures over a city or county. Individual personal exposures are generally unknown. However, the acute studies attempt to relate counts of the number of individuals with a specified health outcome to PM exposures during the day when air pollution was measured in the region or possibly within a few days after such exposure. The

health endpoints reviewed here include death, hospital admissions for respiratory or cardio-pulmonary causes, respiratory symptoms reported in a diary by individuals on a selected panel of people who reside in the region, school absences, and results of standard pulmonary function tests (PFT). Sometimes the health outcome data are divided into demographic subgroups by age, sex, or race. Some studies have also divided the mortality data by primary and contributing causes of death on death certificates, such as respiratory causes or cardio-vascular causes, compared with "control" causes that were believed to have little relation to air pollution.

The strength of acute health effects (short-term exposure-response) studies is that they allow evaluations of a single region or community, comparing the response of a population of individuals on one day with one set of pollution exposures to the response of the same population on another day with a different set of pollution and weather exposures. In general, the daily health effects data should be detrended so that only daily fluctuations in outcome related to daily changes in exposure are evaluated. The detrending includes a variety of techniques to minimize the effects of season and yearly changes in population demographics, as well as control or adjustment for unpredictable variables that may affect health outcome, including weather-related variables and shorter-term random events such as influenza epidemics.

Evidence cited in Chapter 11 suggests that PM or certain PM components may have health effects that are independent of the effects of other criteria pollutants to some extent. However, there does not appear to be any biological marker for distinguishing the full range of PM effects from those of some other air pollutants, since PM does not have a unique chemical characterization and therefore may exhibit a multiplicity of effects. The biological effects or biological interactions resulting from exposure to mixtures of PM and gaseous air pollutants are also not well understood, although it has long been understood that urban and rural airsheds contain such mixtures. The problem of identifying PM effects separately from those of other pollutants using observational data from epidemiology studies is therefore complicated because ambient concentrations of PM may be correlated with those of other pollutants for a variety of reasons. One of two distinct positions may therefore be adopted in interpreting PM epidemiology studies: (1) PM health effects are so thoroughly intertwined with those of other pollutants that PM can serve (at best) as a readily measured index of the total mixture of

pollutants in a region; or (2) due to differences in air pollution mixtures among different communities, and in some cases due to differential time series variations among air pollutants within a region, the effects of PM can be distinguished adequately (albeit not perfectly) from those of gaseous copollutants such as other criteria air pollutants (e.g., CO, O_3, NO_2, etc.). In this chapter we adopt the second point of view: a plausible range of PM effects can be estimated separately from those of of other pollutants by inference, usually depending on statistical analyses of epidemiology data within and between different communities.

Particulate matter effects cannot always be clearly separated from those of other pollutants because of some intrinsic mechanistic factors in observational studies: (1) some gaseous pollutants are precursors of PM components formed as secondary particles; (2) some gaseous pollutants are formed by the same processes that form PM; and (3) weather conditions that affect PM emissions and concentrations at a stationary air monitor are likely to have similar effects on emissions and concentrations of other pollutants. Because of the common causal chains relating PM and other pollutants, it may not be appropriate to describe the PM effects as being "confounded" with those of other pollutants versus distinguishing between possible interactive or independent effects of PM and/or other covarying factors (e.g., copollutants, weather, etc.).

Processes that produce PM may also produce the other pollutants. For example, combustion of fossil fuels used in electrical power generation may produce sulfur dioxide (SO_2) as well as PM, so that emissions of both PM and SO_2 may be high or low at the same time. Moreover, SO_2 may also form atmospheric sulfates, which constitute an important part of fine particle mass in many eastern U.S. cities. Likewise, incomplete combustion of fossil fuels in motor vehicles may directly generate PM and primary pollutants such as carbon monoxide (CO) and nitrogen oxides (NO_x) and indirectly contribute to secondary air pollutants such as ozone (O_3) and nitrates, with nitrates also being a PM component. Weather may be a contributing factor to emissions (e.g., by increasing demand for electric power on very hot summer days or very cold winter days), and meteorological conditions such as inversions also contribute to high concentrations of air pollutants. However, it is important to remember that the potential for confounding of PM effects with weather or other air pollutants does not necessarily mean that confounding actually biased the results in any given study. Confounding must be evaluated on a case-by-case basis. Comparison of estimated PM effects across different communities having

different levels of a potentially confounding factor may help to resolve questions about the role of any given potential confounder. This is discussed in more detail in Section 12.2 below.

Prospective cohort studies follow individuals over an extended period of time. The strength of such studies is that individual risk factors can be accounted for by statistical adjustments or control. Known risk factors for mortality include age, sex, race, occupation, economic status, smoking status, use of alcoholic beverages, and body mass index among others. If the individuals selected are representative of PM exposures across different communities, the effects of individual risk factors can be separated from PM exposure effects. This epidemiologic design also allows (in theory) the evaluation of cumulative exposure to PM over the years, whereas the acute effects study design only allows assessment of effects due to short-term exposure changes. One interesting question is whether there are cumulative effects of chronic PM exposure greater than the sum of daily acute effects, since chronic effects must include short-term effects not subsequently cancelled by short-term improvements. These strengths of prospective cohort studies are greatly reduced if inadequate air pollution measurements are available, so that only crude exposure comparisons across cities or regions can be made.

Population-based studies look only at highly aggregated community health outcomes, such as mortality rates. In some cases, averaging may be advantageous. With no individual-level exposure available, it is only possible to compare different cities by statistical adjustment for demographic and climatological differences and for average differences in levels of air pollutants or other community-wide health risk factors. However, the data for such analyses may be obtained and analyzed relatively easily, and such studies have served a useful historic role in hypothesis generation.

There is still much discussion about the appropriateness of using formal mathematical methods known as "metaanalysis" in research syntheses (Shapiro, 1994). This approach, when applied properly, can provide useful guidance in combining the results of diverse studies. Ultimately, synthesis of the results of the studies reviewed here is clearly desirable, but must be guided by substantive knowledge about the individual studies evaluated. For this reason, important methodological issues that affect pertinent studies are discussed next, followed by evaluation of the studies themselves.

12.2 METHODOLOGICAL CONSIDERATIONS

Studies assessed in this chapter were evaluated for several factors of general importance for interpreting epidemiological studies. These include: (1) exposure measurement errors; (2) misclassification of health outcomes; (3) model specification for acute studies; (4) model specification for chronic studies; (5) covariates and confounders; (6) internal consistency and strength of effects; and (7) plausibility of observed effects. In this section are discussed some methodology issues that more specifically affect the assessment of those PM epidemiology studies evaluated later in this chapter.

12.2.1 Issues in the Analysis of Particulate Matter Epidemiology Studies

There are numerous specific features of epidemiology studies of exposure to airborne particles that largely structure the statistical analyses and interpretation of these studies. Important properties that shape the analyses are: (1) health endpoints typically consist of discrete events in individuals (death, hospital admission for cardiopulmonary symptoms, etc.), although some studies use continuous effects indices such as pulmonary function scores; (2) response variables used in most epidemiology studies consist of the number of discrete events of certain types occurring in a particular community during some interval of time, with a variety of possible endpoints for use in any analysis; (3) individual exposures to air pollution are not typically measured, so that all of the individuals in any study area will be assigned the same air pollution concentration corresponding to the nearest monitor(s) in their community, which is often the only monitor; and (4) since the responses (or effects) to exposure to airborne particle mixtures are very non-specific, relationships between particle exposure and health effects can only be inferred after estimating the contributions of all relevant confounders.

Air pollution studies for particulate matter are usually defined as either *acute* studies or *chronic* studies. Acute studies evaluate effects or responses to changes in air pollution over short intervals of time, typically one day to several days. Chronic studies evaluate effects corresponding to differences in long-term exposure to PM and other air pollutants, usually among different communities. A typical acute study relates changes in the response variable, such as the number of deaths per day for individuals of age at least 65 years, to changes in the PM concentration over the last few days, after adjusting for changes in other variables that affect daily mortality such as temperature and humidity. A typical cross-sectional chronic study

compares annual death rates in a number of cities with different yearly average air pollution concentrations, and adjusts for socioeconomic and demographic differences among cities that may affect mortality rates, such as education, race, and age. Several recent chronic studies used the *prospective cohort study design*. In a prospective cohort study, individuals are recruited into the study and followed over an extended period of time, ideally many years. Even though air pollution is still characterized by community-level measurements in these prospective cohort studies, the individual responses may be adjusted for individual risk factors such as age, cigarette smoking, and possible occupational exposures.

Each kind of PM epidemiology study has certain advantages and disadvantages. Acute studies deal with short-term responses to changes in air pollution concentrations and are not confounded with long-term changes in population demographics, behavior, or changes in exposure distribution, although statistical analyses of long time series may require such adjustments. Also, while all epidemiology studies that use community air monitors face the problem that different individuals in a community may have different individual exposures, it is plausible that average *relative changes* in exposure from one day to the next may be adequately characterized by the relative changes at a single community air monitor. On the other hand, acute studies cannot offer any method for dealing with cumulative or long-term effects of PM exposure, since responses that may be due to months or years of past PM exposures would not necessarily be fully reflected in acute exposure-response associations.

One of the unresolved issues in the analysis of mortality data is the extent of shortening of life (or the prematurity of death) associated with ambient PM exposures. Daily mortality time series are analyzed so as to identify responses to changes in air pollution that have occurred within the last few days. If these acute studies are analyzed correctly, the analysis must necessarily eliminate the longer-term effects that occur over time scales longer than several weeks. Thus, acute studies are necessarily limited in their ability to detect displacement of mortality over periods of time longer than several days. However, several studies have investigated patterns of autocorrelation of mortality over periods of a few days. Significant negative autocorrelations are consistent with the hypothesis that excess mortality on one day may have depleted a pool of potentially susceptible subjects on subsequent days (Spix et al., 1994; Wyzga and Lipfert, 1995b; Cifuentes and Lave, 1996). On the other hand, longer-term

mortality studies provide results which are suggestive of additional chronic effects consistent with excess mortality in which some subjects may die prematurely by one or more years.

In principle, chronic studies should allow the assessment of total health effects, since the effect of PM exposure will includes both the detectable acute responses as well as the cumulative effects that are not detected by an acute study. Thus, chronic studies should, for example, be able to detect any additional chronic PM exposure effects beyond acute exposure mortality displacement effects of a few days or a few weeks (sometimes called "harvesting"). In practice, cross-sectional chronic studies comparing different communities must be adjusted for a wide variety of factors that may affect mortality rates, so that differences in community pollution exposure may be confounded with other differences that affect community mortality rates or other community-based health outcome indices. Prospective cohort studies are less subject to confounding by community-level factors. However, unmeasured differences in individual exposure to PM within a community are not necessarily independent of other individual risk factors and could be confounded with these factors. It may also be hard to obtain long-term individual exposure histories. Since the causes of death that are most often associated with excess PM exposure are in the respiratory and cardiovascular categories, the prospective cohort study design has the potential to be superior to the cross-sectional design in its ability to control for other highly significant individual risk factors such as cigarette smoking and occupational exposure. However, unmeasured or inadequately measured individual risk factors can diminish this advantage.

While different kinds of epidemiology studies have illuminated different aspects of PM exposure, the acute mortality and morbidity studies have provided the strongest and most consistent evidence for health effects from PM exposure. Results have been generally consistent across different studies by different investigators, and the results have been robust to reanalyses using different model specifications and different statistical analysis methods. Because the responses are usually in the form of counts (deaths, hospital admissions), it is convenient to characterize results in terms of relative risks (RR) corresponding to a specific PM increment, say 50 $\mu g/m^3$ PM_{10} or 100 $\mu g/m^3$ TSP. The excess risk (RR - 1) for PM exposure is typically much higher among the elderly than among the entire population, typically 2 or 3 times higher for respiratory causes than for all causes, and typically somewhat higher for cardiovascular causes than for all causes. This pattern is plausible for an air pollutant. There is also some coherence

or qualitative consistency between mortality rates and hospital admission rates, with several times as many daily hospital admissions likely to occur as deaths, especially among the elderly. Evaluation of respiratory function and/or symptom changes in relation to daily PM exposures are also supportive of the potential for acute morbidity effects to occur in response to short-term PM exposures.

Cross-sectional studies also tend to be indicative of PM health effects, but the evidence is less conclusive and the effects of other pollutants cannot be as clearly separated from the PM effects. The prospective cohort studies of adult mortality are also supportive of the results of the acute studies. Quantitative consistency is based on the result that the RR estimates from two of the prospective cohort studies are somewhat larger than the corresponding RR estimates from any of the acute mortality studies, as expected if the prospective cohort studies picked up some additional mortality from cumulative PM exposure not detectable in the acute mortality studies.

In the following subsections are reviewed methodological issues that most strongly affect the structure of the statistical analyses used in the subsequently reviewed PM epidemiology studies and the conclusions that can be drawn from these analyses. Most of these issues involve the specification of the concentration-response or dose-response models. The most important issues are the specification of the models for the effects of PM and other pollutants, and for methods by which the data should be adjusted for weather and for other time trends. One particular concern has been the shape of the concentration-response function for PM, with special attention to a possible PM "threshold" concentration and other nonlinearities. Other important substantive issues are discussed later in the chapter, including the differences in averaging times or lags used in the various acute mortality and morbidity models, the possible differences in health effects between fine particles ($PM_{2.5}$ or smaller) and thoracic coarse particles (PM_{10} - $PM_{2.5}$), and effects of chemical composition or acidity of particles.

12.2.2 A Historical Perspective on Air Pollution Modeling

Daily Time Series Models

The analysis of air pollution time series data has proceeded through three broad phases of analytical strategy over the last several decades. The first phase was largely based on "classical" time series and regression analysis methods. These methods generally assumed that the response variable was approximately normally distributed or could be transformed to approximate a

normally distributed variable (for example, by using the logarithm of the mortality rate or the square root of daily counts). Time series structure was focussed on the autoregressive nature of the response variable, and was addressed either by assuming autoregressive or moving average residuals. A common technique was to adjust the mortality time series for the effects of longer-term trends ("detrending") by subtracting out appropriate moving averages of the response variable, most commonly a 15-day moving average centered on the current day's response (Schimmel, 1978; Mazumdar et al., 1981, 1982; Mazumdar and Sussman, 1983; Ostro, 1984). There was some interest in evaluating other "filters" of the data, or in evaluating detrending in the frequency domain using spectral analysis techniques (Shumway et al., 1983, 1988). Similar analyses of time series of the regression predictors or covariates, such as air pollution concentrations and weather variables, were sometimes also done. These techniques were refined and used extensively in the analyses of the mortality series for the 1958 to 1972 London winters (Schwartz and Marcus, 1986, 1990) that played an important role in the 1986 Criteria Document Addendum and the setting of the 1987 PM_{10} NAAQS.

Since that time there has been a substantial shift in the data analysis paradigm. This second phase of analytical strategy is based on the recognition that the counts of discrete events used as responses (such as daily deaths or hospital admissions) are more appropriately modelled as Poisson variables, and that temporal structure is more appropriately included by modeling correlation structure in covariates and in over-dispersion or random variation in the daily mean number function. These analyses have typically been carried out using recently developed methods for longitudinal analysis of counting data (Zeger and Liang, 1986) which depend on an iterative Generalized Estimating Equation (GEE) approach. Some concerns about the validity of the GEE methods were resolved at the workshop on air pollution mortality sponsored by EPA in November, 1994 and by continuing research in statistical theory and methodology (Samet et al., 1995). Many investigators now believe that the Poisson GEE methods provide reasonable estimates of the effect size or regression coefficients for air pollution and other covariates in correctly specified models. There is also reason to believe that the statistical uncertainty of the effect size estimates is also accurately characterized by GEE methods, whether the uncertainty is characterized by asymptotic standard errors, t-statistics, confidence intervals, or P-values (significance levels). However, other statistical methodologies may also be useful.

A third wave of statistical modeling approach seems to be emerging in which the concentration-response functions and other aspects of model specification are not being restricted to explicit parametric functions defined by the analyst. This approach is based on the fact that there really is not any explicit parametric model for the effects of weather-related variables or air pollution on mortality or hospital admissions. So-called nonparametric regression models allow determination of an empirical relationship between response and predictors. Current implementation of methods such as Local Estimation and Scatterplot Smoothing (LOESS) smoothers and generalized additive models (GAM) allow very detailed exploration of air pollution epidemiology data to derive good-fitting models (Schwartz, 1994g,h). Furthermore, classical visual methods for evaluating regression residuals can sometimes be applied, and global goodness-of-fit statistics for the model allow quantitative assessment.

The nonparametric modeling approach allows fitting and visual checking of different concentration-response models. Unfortunately, there is a considerable loss in the ability to easily compare models for different data sets or subsets of data. For example, in comparing the estimated effects of, say, exposure to 100 $\mu g/m^3$ PM_{10} versus 150 $\mu g/m^3$ PM_{10}, linear models for log-mortality can be compared in terms of the regression coefficients or, in this Chapter, in terms of relative risks (RR) per 50 $\mu g/m^3$ difference. The nonparametric models can also be compared across this range, but current computer program implementations do not allow assessment of the uncertainty of the RR estimate across this range. For linear models, the same RR estimate applies to the comparison of 200 $\mu g/m^3$ PM_{10} versus 150 $\mu g/m^3$ PM_{10}, whereas the RR for each different range of 50 $\mu g/m^3$ must be calculated anew using the nonparametric concentration-response model. Of course, if the response to PM or other predictors really is nonlinear, this may be advantageous. On the other hand, the comparisons of response in different studies, in different cities, and in different years or seasons must be made on a similar case-by-case comparison basis.

Some classes of nonparametric models are really "parametric", such as GAM models that are cubic splines whose parameters are the knots or join points of cubic polynomial segments, and the polynomial coefficients in each segment. These parameters and their statistical uncertainty are generally not accessible to the analyst using current computer implementations.

This is not to say that the statistical analyses should be limited to linear, log-linear, piecewise linear or other simple forms that may not fit the response data. However, it is important to point out that in most cases in which concentration-response or dose-response function models are derived from basic biological principles, the parameters in the function may have a specific biological meaning or interpretation that illuminates some underlying process or mechanism. Conversely, the nonparametric model may fit better than a simple parametric model and illustrate important failures in that model and in assumed mechanisms.

This point is illustrated in detail in Section 12.6.2. The two-dimensional nonparametric surfaces fitted by Samet et al. (1995) to TSP and SO_2 for Philadelphia daily mortality data from 1973 to 1980 differ significantly from the standard additive linear model for TSP and SO_2. Interpretations of the role of copollutants in PM models depend on the joint estimates of regression coefficients in additive linear models for PM with and without copollutants. If the additive linear model does not correctly specify the true relationship between the response, PM index, and the other pollutants or covariates, then these interpretations may not be correct.

Thus, the choice of different statistical models may lead to substantive differences in interpretation. In general, however, use of different models within a wide range of reasonable model specifications has produced generally similar conclusions in most studies, as demonstrated in Section 12.6.3.

Statistical Methods for Population-Based Studies

Linear and nonlinear regression methods are generally used when the response variable is a population-based index of community health, such as the annual death rate in the community, possibly stratified by age and cause of death. Statistical methods are similar to those in other applications of regression models in epidemiology, but the problems of confounding of multiple pollutants and of sociodemographic factors have been addressed explicitly in a variety of ways. If the model is specified as a linear model (typically, logarithm of death rate versus logarithm of air pollutant concentrations) and there are no substantial misspecifications of functional dependence or omission of interaction terms, then confounding of variables is often manifested as collinearity of the variables. Some authors have attempted to deal with collinearity by use of biased estimation techniques, such as ridge regression, but the usual technique is to see whether or not the estimated regression coefficient is substantially changed by the inclusion of other pollutants or other potentially confounding demographic factors. The sensitivity of the effect size estimate is not only an easily understood criteria, it is also technically among the most effective diagnostic criteria for potential confounders (Mickey and Greenland, 1989). For this reason, most investigators usually report the results of multiple models, with and without potential confounders.

Statistical Models for Prospective Cohort Studies

The response variables in prospective cohort studies can be discrete events (death, hospital admission) or continuous measurements (PFT values) in individual subjects. Discrete event analyses can be carried out using methods for binary data such as logistic regression, or methods such as the Cox proportional hazards regression model if time to the event is known. The modelling problems are similar to those encountered in the population-based analyses, particularly the role of confounding and the use of fixed sets of predictors as opposed to data-driven search procedures such as stepwise regression.

12.2.3 Model-Building Strategies for Pollution and Weather Variables

The specification of models relating acute health effects to air pollutants and to other variables or covariates is particularly difficult in the case of PM indices, because of the relative absence of any *a priori* theoretical basis for a concentration-response or dose-response

relationship. The extensive statistical modelling of these relationships has therefore been carried out in a much more exploratory manner than is typical for other environmental pollutants. This has been facilitated computationally by the availability of sophisticated modern statistical curve-fitting procedures that do not require specification of parametric dose-response or concentration-response functions. Selection of variables for analysis is based on substantive hypothesis, however, even if functional specifications are not. Paradoxically, the relative convenience of curve-fitting software programs has failed to illuminate underlying mechanisms or processes. In many applications, the nonparametric relationships between PM and response (e.g., logarithm of expected mortality) has been so nearly linear that a linear model provides almost as good a fit to the data as does the empirical smooth curve. However, in the HEI reanalyses (Samet et al., 1995) of the Philadelphia TSP and SO_2 data which includes the effects of both pollutants, there were significant deviations from a purely additive linear model and more complex models appear to be needed to more fully understand the relationship between response (excess mortality) and air pollution.

The four major approaches to developing statistical relationships have been applied in rather similar ways to air pollutants, to covariates related to weather, and to calendar time as predictor variables for the response (mortality or log mortality). The four general approaches are:

(1) fit a parametric regression model with the predictor variable;

(2) divide the predictor variable into intervals or ranges (deciles, quintiles, quartiles, fixed size intervals, etc.) and use membership in the interval as a categorical or dummy variable predictor;

(3) fit a smooth nonparametric regression model with the predictor variable;

(4) divide the data into subsets by season, year, range of predictor values etc., and fit the above models within each subset.

Fitting Parametric Regression Models

Linear models have most often been used for PM and other pollutants (denoted generically OP). In some applications, a linear model with the logarithmic transform of the pollution variable was used. A piecewise linear function was used by Cifuentes and Lave (1996) and is discussed in more detail in Section 12.6.

Various functions have been used for weather-related variables, including quadratic functions (Li and Roth, 1995) and "absolute deviation" or V-shaped piecewise linear functions of temperature. The relationship of mortality to weather is clearly nonlinear, except possibly within a season (e.g., Schwartz and Marcus, 1990), and linear models are not generally used.

Long-term trends in mortality and hospital admissions are evident in most multi-year studies, and detrending is clearly needed. Linear models with calendar time as the predictor are often used, but recent reanalyses of the Philadelphia data (Schwartz, 1996) suggest that a quadratic model may be more appropriate. Seasonal variations within a year have sometimes been modeled using a Fourier series, that is, a sequence of sine and cosine functions of time of year.

Some parametric models have important causal interpretations. For example, a piecewise linear function of PM with 0 slope for PM below a specified critical concentration c, and positive slope above c, would be interpreted as a model suggesting that there is a "threshold" for PM at concentration c, and that PM concentrations below c pose no risk.

Dividing Predictor Variables into Ranges or Intervals

A number of investigators have recognized the possibility of a nonlinear concentration-response relationship and have attempted to circumvent the problem of identifying the parametric form of the relationship by using the PM or other pollution index as a categorical variable, with values in an interval being indicated by a dummy variable (Schwartz and Dockery, 1992a,b). The usual basis for membership is an empirical quantile classification of the PM index, such as by quartiles or quintiles. This procedure appears to introduce some additional measurement error into an epidemiology modeling problem in which exposure measurement error is already a concern.

Classification of weather-related variables by interval membership has similar advantages and disadvantages. One advantage is that combinations of weather variables for different conditions can be included as simple interaction terms, for example "hot wet day" is included by using the product of indicator variables for "hot" and "wet" as an additional predictor variable. A much more sophisticated approach to grouping weather variables is developed by the construction of "synoptic climatologic classes" (Kalkstein et al., 1995).

Time trends can be similarly coded, with separate indicators for season and for year, and season within year as the product of season and year indicators. Indicator variables for day of the week are also convenient.

Recent developments in statistical software and theory allows the fitting of regression models in which the functional parametric relationship between the response and some or all the predictors may not be specified. One class of smooth nonparametric model, the so-called cubic spline method, involves fitting piecewise cubic functions over certain ranges of the predictor variables, with requirements for continuity of the fitted function at the join points (or knots) and additional global requirements for smoothness of the fitted function as defined by the integrated square of the second derivative of the function over an interval. This method is intrinsically nonlinear and iterative when the join points (analogous to the threshold concentration c in a piecewise linear model) are estimated from the data and are not specified in advance. Other methods, such as kernel-type regression smoothers, may also be used. Examples of nonparametric smoothing were presented by Schwartz (1994g,h). One- and two-dimensional nonparametric regression models with TSP and SO_2 have recently been presented in the Health Effects Institute (Samet et al., 1995) reanalyses of Philadelphia data, and are discussed below in more detail. These models allow much better assessment of nonlinearities in the concentration-response model, but do not allow a convenient basis for comparison of air pollution relationships in different cities or at different times.

Nonparametric regression models may be particularly useful in acute response studies in which the purpose of the model is to eliminate the effects of weather, season, and long-term time trends from assessment of short-term changes in mortality or hospital admissions in response to short-term changes in air pollution. The object is not to get the "right" model for weather, for example, but simply to adjust short-term fluctuations in response for changes in these covariates over time scales longer than a few days.

Dividing the Data into Subsets

This approach is an alternative to using models with all of the data. Subset models are similar to the other models, but without indicator variables or parametric or non parametric detrending to account for the fact that there may be somewhat different relationships between the response and air pollution variables in different subsets of the data set, such as seasonal

differences. Other subset approaches include separate analyses for hot days (Wyzga and Lipfert, 1995b) or for "compliance days" (e.g., for $PM_{10} < 150\ \mu g/m^3$). The use of non-contiguous days in subset analyses may complicate the time-series aspects of the analyses. Since any subset analysis is likely to substantially reduce the number of data points (days of data) in the data set, the statistical significance of any effect is likely to be attenuated in a subset analysis. As shown below, data sets with fewer than about 600 to 800 days of data have relatively low power to detect a statistically significant PM effect even if it exists.

12.2.4 Concentration-Response Models for Particulate Matter

The concentration-response relationship assumed in most of the recent analyses is at least additive (as in "generalized additive models") and often simply linear as well as additive. That is, if E(Y) represents the expected number of deaths per day, or expected number of hospital admissions per day, then the model assumed by most recent studies is generally of the form

$$\log(E(Y)) = XB + s(PM) + S(OP)$$

where s(PM) is a smooth function of the particulate matter index (PM) and S(OP) is another smooth function of the other pollutant(s) in the model. All of the other covariate adjustments are denoted, generically, XB. There has so far been little consideration of piecewise linear models with a join point at concentration PM = c (i.e., a "linear spline"), with the general form:

$$s(PM) = a\ PM \qquad \text{if } PM < c,$$
$$s(PM) = b\ (PM - c) + ac \qquad \text{if } PM > c.$$

A special case is the model with a "threshold" at c, of the form (a = 0):

$$s(PM) = 0 \qquad \text{if } PM < c,$$
$$s(PM) = b\ (PM - c) \qquad \text{if } PM > c.$$

The paper by Cifuentes and Lave (1996) is an informative application of piecewise linear modelling, and is discussed in some detail in Section 12.6. However, as noted in Section 12.2.5,

it is very difficult to distinguish threshold model from other nonlinear models, and such an abrupt nonlinearity may be biologically unrealistic.

Even less work has been done in investigating interaction models among pollutants, which are intrinsically non-additive. These are also discussed in Section 12.6, in connection with the recent Health Effects Institute analyses (Samet et al., 1995) of the relationships between mortality, TSP, and SO_2 in Philadelphia.

Most of the responses or adverse health effects are quantified in this chapter by the term "relative risk" or "risk rate", denoted by RR. This term is used here to denote expected excesses in mortality rates, hospital admissions rates, and so on over baseline levels as a function of specified increments in air pollution. This approach allows comparison of air pollution effects without consideration of baseline differences in rates in different communities with differing socioeconomic properties, different prevalence of illness, or different climate. If the estimated effect of the air pollution exposure is characterized by the regression coefficient denoted b in the above model, then the relative risk RR, for a specified PM increment (denoted PMinc) is:

$$RR = \exp (b\ PMinc).$$

Since most statistical estimates of b also allow a calculated (asymptotic) standard error for *b*, denoted se(b), the lower confidence limit (LCL) and upper confidence limit (UCL) for RR are:

$$LCL = \exp ((b - t\ se(b))\ Pminc),\ UCL = \exp ((b+t\ se(b))\ PMinc).$$

The value of t for a 95 percent confidence interval is about 2. The values of Pminc depend on the PM index: 100 $\mu g/m^3$ for TSP, 50 $\mu g/m^3$ for PM_{10}, 25 $\mu g/m^3$ for $PM_{2.5}$, etc.

An alternative approach to characterizing response to PM involves fitting a somewhat different model. If the concentration response model is fitted in log-log form, as is common for most population-based cross-sectional analyses, then the regression coefficient is often called an elasticity. If the elasticity for PM is denoted k, then the model fitted is usually of the form

$$E(\log(Y)) = XB + k \log (PM)$$

The parameter k can be thought of as the relative change in response per relative change in PM, for example the percentage change expected in Y for a one percent change in PM. The elasticity

k is not directly comparable to a log-linear regression coefficient b. The log-linear form of the model can often be approximately compared by calculating an "elasticity at the mean":

Elasticity at the mean = b (mean of PM) / (Mean of Y).

In general, the elasticity at the mean will not be the same as an estimated k. Lipfert and Wyzga (1995b,c) make extensive use of elasticity as an index of risk.

12.2.5 Modeling Thresholds

The existence of thresholds can be argued both biologically and statistically. The biological arguments have been given by several authors, including Stokinger (1972), Dinman (1972), and Waldron (1974). Methods for estimating threshold models have been given by several authors including Quandt (1958), Hudson (1966), Hasselblad et al. (1976), Crump (1984a,b), Crump and Howe (1985), Cox (1987), and Ulm (1991). However, the concept of a threshold may be confused with the concept of a non-zero background. A threshold model starts out completely flat, possibly above zero, and at some point begins to curve upwards. A non-zero background model begins above zero and continually curves upward. However when fitting data, "... an additive background dose is generally not distinguishable from a threshold" (Cox, 1987). Cox (1987) gives 10 real data sets where thresholds have been estimated, and in every one of them it is possible to fit a non-threshold model which fits nearly as well. Thus, for epidemiologic studies, the question of thresholds may be difficult to resolve because of difficulties in estimation. When there is substantial measurement error in the exposure variable or heterogeneity in threshold values in a population, it may not be possible to identify a threshold using aggregate response data such as mortality counts or hospital admissions.

Many epidemiological studies reviewed in this section were structured to develop linear or log-linear models with no such threshold, and in many cases, this assumption has been supported by the data plots presented. However, it has also been shown that it may be difficult to distinguish among alternative regression models with confidence, presumably because the main outlying observations are controlled by factors not included in the model. In such cases, linear and threshold models may have essentially equivalent predictive power. In any event, the epidemiology studies reviewed in this chapter have limited power to identify or detect thresholds. Biological and mechanistic hypotheses about thresholds have not yet reached the

stage of quantitation. While many of the epidemiology analyses clearly estimate higher risks of effects at higher PM levels than at lower levels, it is currently not feasible to preclude the possibility that such effects may have threshold-like flattening of response in the midrange of current ambient exposures.

The detection of thresholds for health endpoints used in PM epidemiology studies would be technically difficult even if exact biological thresholds existed, for two reasons: (1) intrinsic biological variability; and (2) measurement error in exposure and other covariates. The effect of biological variability may be seen in a conceptual model in which each individual has at any given moment a specific PM exposure concentration which, if exceeded, would kill the person or send him or her to the hospital with specific symptoms. It is likely that the individual's susceptibility to PM is itself changing over time, reflecting disease state and other physiological conditions and environmental stresses, so that a specific PM concentration that might kill the individual at one time would not do so at some other time. Inter-individual differences in susceptibility are also to be expected, in addition to intra-individual variability over time. When individual thresholds are distributed over some range of values, the composite apparent relationship between response and PM concentration would not appear to have a threshold.

The second reason why thresholds would be difficult to detect is that individual PM exposures are not known, so that the use of community PM concentration as a predictor introduces an unknown but possibly large statistical "measurement error". It has long been known that measurement error in regression models can change the apparent shape of a regression model specification, from truly linear to apparently nonlinear as well as from truly nonlinear to apparently linear. This has long been known to statisticians, for example, in a widely cited paper by Cochran (1968), based on a theoretical analysis by Lindley (1947), but is only rarely mentioned in the epidemiology literature (Gilbert, 1984). Lipfert and Wyzga (1995b) have studied some aspects of this using computer simulation methods with piecewise linear threshold models and parameters relevant to TSP mortality studies. Thresholds often become undetectable, even when they really exist and a threshold model is correctly specified, if the predictor is measured with statistical error. Thomas et al. (1993) review other issues associated with measurment error problems.

12.2.6 Confounders and Choice of Covariates

Confounders in epidemiologic analyses must: (1) be an independent risk factor for the outcome; (2) be associated with the exposure variable; and (3) not be an intermediate step in the causal path between the exposure and the outcome (Rothman, 1986). The risk factor need not be causal in this case. Thus, many weather variables, as well as some co-pollutants, may qualify as potential confounders for PM-mortality or morbidity associations.

The causality of various weather and pollution variables may or may not be clear, however. For example, an extreme (hot or cold) temperature is known to cause excess mortality, and laboratory human and animal studies support biologically plausible mechanisms for such observations. Thus, simultaneous inclusion of temperature and pollution variables in a time-series regression is crucial, although there is some chance that this may result in under-estimation of pollution coefficients because temperature is also correlated with meteorological conditions that cause air pollution build-up. Wind speed is clearly a good predictor of air pollution build-up, but is not directly causally related to health outcomes. Therefore, inclusion of wind speed in mortality/morbidity regressions is not recommended for air pollution epidemiology unless it is part of an appropriate combined index of weather patterns. Barometric pressure is an example of another variable whose effect (within the range of day-to-day variation) on physiological functions is not clear (Tromp, 1980). It is associated with certain physiological changes (such as shift in blood pressure), but this may be due to its association with temperature change, which is also related to change in blood pressure. Barometric pressure is also correlated with air pollution levels. Thus, while there is a need to address potential confounders, care must be taken that the regression model selected is not over-specified.

Common air pollution variables, such as SO_2, O_3, NO_2, and CO are all known to cause various types of health effects and physiological changes. However, whether short-term exposures to commonly occurring levels of these pollutants cause premature deaths, independent of PM, is not known. In fact, some of these pollutants may be co-factors, rather than confounders. Possibility of synergistic effects of these pollutants are almost never examined or discussed in the current literature. The fact that PM is not a chemically specific pollution index makes the issue of confounding even more complicated. For example, PM may include sulfates, which are formed from SO_2. Then, SO_2 becomes part of the causal pathway of PM effects, and is no longer a confounder for this PM. Also, if reduction of PM results in reduction of co-pollutants, a PM regression coefficient derived from a multi-pollutant regression model may

give misleading results for policy analysis. In addition, it is unlikely that a mixture of these pollutants affects human health in a simple additive manner. Thus, there is an inherent limitation in the prevailing explanatory multi-pollutant regression approaches.

On a day-to-day basis, the concentrations of these air pollutants, as well as PM, may be correlated to varying degrees, due to the meteorological conditions that control dispersion of these pollutants. Care must therefore be taken when including these correlated pollution variables in a health effect regression, as their coefficients may be unstable. Furthermore, the significance of coefficients for each variable may be influenced by their individual measurement errors, rather than their causal strengths. Thus, without external information regarding differential error and some description of collinearity among the covariates, interpretation of these multiple regressions with collinear variables can be misleading.

Under circumstances where various collinear variables are present and each one of the pollutants is suspected of causality to differing degrees, a single pollutant model may result in over-estimation of the coefficient for that pollutant, while a multiple pollutant model may result in under-estimation of each pollutant's coefficient. Separation of possible effects from these various correlated pollutants may be difficult from a single study, but may be possible by evaluating the consistency of coefficients across studies in which the levels and the extent of collinearity of co-pollutants vary. To facilitate such collective understanding (or even meta-analysis), it is crucial for each study to include systematic description of collinearity among the covariates (e.g., correlation of the estimated parameters), levels of each pollutant, and discussion of biological plausibility for each variable at the observed ambient levels.

While the parsimony of a model is generally desirable, blind reliance on the automatic variable selection schemes based on the F-statistic, such as stepwise regressions, or the use of other criteria, based on residual error and number of parameters (Akaike, 1973; Schwarz, 1978) is not appropriate for epidemiologic purposes, as the objective is not to develop a parsimonious model, but to assess the impact of pollution while adequately 'controlling' for other covariates.

12.2.7 Confounding in Cross-Sectional Analysis

Development of an appropriate regression model for cross-sectional (spatial) analysis is fraught with many of the same difficulties found with time-series (temporal) analyses. The central problem (as in all multiple regressions) is to "identify the true confounders without

overadjusting" (Leviton et al., 1993). With spatial analysis, adjustments must be made for spatially varying factors that affect (or are correlated with) air pollution and that affect longevity. Whereas many factors affect longevity (age, genetics, race, poverty, education, alcohol consumption, water quality, climate, lifestyle, for example), the extent to which any of these factors may be correlated with air quality varies with the scale being considered. In most cases, the intercorrelations are indirect; for example, industrial locations have more air pollution and often the people who live there are on the lower end of the socioeconomic scale. Thus, economic factors may be a confounder because of their additional health risk impacts. Regional air quality trends arise from climatic factors and from the types of fuels and industrial activities present. However, ways of accomplishing "spatial detrending" have not been considered in much detail and it may not be possible to fully disentangle regional air pollution from other regional characteristics; Lipfert (1994a) showed, for example, that SO_4^{2-} was correlated with regional factors while TSP was correlated with local characteristics.

In a prospective cohort study, each individual should be characterized according to relevant demographic and lifestyle attributes, which not only provides control in a multi-variate model but also allows for stratification by attribute. In an ideal situation, the effects of air pollution can then be readily examined by regressing survival against individual air pollution exposures. In population-based (ecological) studies, entire communities are classified or described by these attributes in addition to their average air pollution levels. The regression must then deal with the entire communities rather than individuals, a situation that could give rise to the well-known ecological fallacy. To the extent that both of these types of analyses are forced to use the same types of spatially-averaged air quality data, the differences between them are due to the ways in which they handle the "control" variables. In the absence of interactions among these variables on an individual level, the two types of analyses should produce comparable results.

At present, the selection of appropriate control variables appears to be somewhat more of an art than a science. First, many of them are surrogates for the actual effects on health and longevity. For example, income cannot purchase good health directly but increased income may allow access to better medical care; and more education may not only lead to higher income, it may also allow one to make better use of the resources available. Data on diet, genetic susceptibility, and many lifestyle parameters are not available for individuals or local communities; data on broad regional trends may be available in selected instances. The

determinants of good health may change over time (such as quitting smoking, taking up an exercise program, etc.); using data obtained at entry to a prospective study might later lead to misclassification errors for some participants.

Defining a mortality model requires selecting the appropriate control variables; the various extant cross-sectional studies have devised different ways of accomplishing this. By and large, the prospective studies have been limited to the parameters that were selected at entry to the study, many years ago in most cases. Population-based studies have more flexibility because of the myriad sources of information describing communities, although most of them are surrogates for the real variables that affect health. As pointed out by Ware et al. (1981), "it is likely that the effects of variables such as personal habits, occupational exposure, and medical care cannot be fully quantified in this way. If any of these factors covaries with air pollution levels, a spuriously large effect will be attributed to air pollution." More formally, errors in estimating the true relationships between outcome and confounders will be reflected as artifacts in the observed relationships between outcome and air pollution. Given the diversity of approaches to the problem, some simple caveats arise:

1. Candidate variables should have reasonable expectation of a causal relationship with the outcome, based on exogenous findings. Variables such as elevation or rainfall do not appear to meet this standard, for example, and purely geographic variables such as latitude or region are probably better used to define stratified subsets.

2. Given the implied importance of the "correct" specification of potential confounders, results should be presented for these variables and compared with a priori expectations.

3. Consistency of results with a variety of models, including both optimized (such as stepwise) and defined (forced entry) types, is required to provide confidence in the conclusions.

12.3 HUMAN HEALTH EFFECTS ASSOCIATED WITH SHORT-TERM PARTICULATE MATTER EXPOSURE

Some of the earliest indications that short-term ambient air particulate matter or acid aerosols exposure may be associated with human health effects were derived from the

investigation of historically well-known, major air pollution episode events. These include the Meuse Valley (Belgium), Donora, PA (USA), and London (UK) episodes.

Firket (1931) described the December 1930 fog in the Meuse Valley and the morbidity and mortality related to it. More than 60 persons died from this fog and several hundred suffered respiratory problems, with many of the latter complicated by cardiovascular insufficiency. The mortality rate during the fog was more than 10 times higher than normal. Those persons especially affected were the elderly, those suffering from asthma, heart patients, and other debilitated individuals. Most children were not allowed outside during the fog and few attended school. Unfortunately, no actual measurements of pollutants in ambient air during the episode are available by which to establish clearly their relative roles in producing the observed health effects, but high PM levels were obviously present.

Schrenk et al. (1949) later reported on the atmospheric pollutants and health effects associated with the Donora smog episode of October 1948. A total of 5,910 persons (or 42.7%) of the Donora population experienced some effect. The air pollutant-laden fog lasted from the 28th to the 30th of October, and during a 2-week period 20 deaths occurred, 18 of them being attributed to the fog. An extensive investigation by the U.S. Public Health Service concluded that the health effects observed were mainly due to an irritation of the respiratory tract. Mild upper respiratory tract symptoms were evenly distributed across all age groups and, on average, were of less than four days duration. Cough was the most predominant symptom; it occurred in one-third of the population and was evenly distributed through all age groups. Dyspnea (difficulty in breathing) was the most frequent symptom in the more severely affected, being reported by 12% of the population, with a steep rise as age progressed to 55 years; above this age, more than half of the persons affected complained of dyspnea. While no single substance could be clearly identified as being responsible for the October 1948 episode, the observed health effects syndrome seemed most likely to have been produced by two or more of the contaminants, i.e., SO_2 and its oxidation products together with PM, as among the more significant highly elevated contaminants present.

Based on the Meuse Valley mortality rate, Firket (1931) estimated that 3,179 sudden deaths would likely occur if a pollutant fog similar to the Meuse Valley one occurred in London. An estimated 4,000 deaths did later indeed occur during the London Fog of 1952, as noted by Martin (1964). During the 1952 fog, evidence of bronchial irritation, dyspnea, bronchospasm

and, in some cases, cyanosis is clear from hospital records and from the reports of general practitioners; and a considerable increase in sudden deaths from respiratory and cardiovascular conditions occurred. The nature of these sudden deaths remains a matter for speculation since no specific cause was found at autopsy. Evidence of irritation of the respiratory tract was, however, frequently found and it is not unreasonable to suppose that acute hypoxia due either to bronchospasm or exudate in the respiratory tract was an important factor. Also, the United Kingdom Ministry of Health (1954) reported that in the presence of moisture, aided perhaps by the surface activity of minute solid particles in fog, some sulfur dioxide is oxidized to trioxide. It is possible that sulfur trioxide, dissolved as sulfuric acid in fog droplets, appreciably augmented the harmful effects of PM and/or other pollutants.

The occurrence of the above episodes and resulting marked increases in mortality and morbidity associated with acute exposures to very high concentrations of air pollutants (notably including PM and SO_2 in the mix):

(1) left little doubt about causality in regard to the induction of serious health effects by very high concentrations of particle-laden air pollutant mixtures;

(2) stimulated the establishment of air monitoring networks in major urban areas and control measures to reduce air pollution; and

(3) stimulated research to identify key causative agents contributing to urban air pollution effects and to characterize associated exposure-response relationships.

Besides evaluating mortality associated with major episodes, the 1982 criteria document (U.S. Environmental Protection Agency, 1982a) also focused on epidemiology studies of more moderate day-to-day variations in mortality within large cities in relation to PM pollution. Evaluating risks of mortality at lower exposure levels, the 1982 criteria document concluded that studies conducted in London, England by Martin and Bradley (1960) and Martin (1964) yielded useful, credible bases by which to derive conclusions concerning quantitative exposure-effect relationships. The 1986 addendum to the 1982 criteria document (U.S. Environmental Protection Agency, 1986a) also considered several additional acute exposure mortality analyses of London data for the 1958 to 1959 through 1971 to 1972 winter periods, conducted by Mazumdar et al. (1982), Ostro (1984), Shumway et al. (1983), and by U.S. EPA (later published in Schwartz and Marcus, 1990). After assessing these various re-analyses and the previously

reviewed London results, the following conclusions were drawn (U.S. Environmental Protection Agency, 1986a,b):

(1) Markedly increased mortality occurred, mainly among the elderly and chronically ill, in association with BS and SO_2 concentrations above 1,000 $\mu g/m^3$, especially during episodes with such pollutant elevations over several consecutive days;

(2) During such episodes, coincident high humidity or fog was also likely important, possibly by providing conditions leading to formation of H_2SO_4 or other acidic aerosols;

(3) Increased risk of mortality is associated with exposure to BS and SO_2 levels in the range of 500 to 1,000 $\mu g/m^3$, for SO_2 most clearly at concentrations in excess of $\approx$700 $\mu g/m^3$; and

(4) Convincing evidence indicates that relatively small, but statistically significant, increases in mortality risk exist at BS (but not SO_2) levels below 500 $\mu g/m^3$, with no indications of any specific threshold level yet demonstrated at lower concentrations of BS (e.g., at $\leq$150 $\mu g/m^3$). However, precise quantitative specification of lower PM levels associated with mortality is not possible, nor can one rule out potential contributions of other possible confounding variables at these low PM levels.

The extensive epidemiological research that ensued has advanced our knowledge regarding the above issues, especially the roles played by PM and SO_2 in mortality and morbidity associated with non-episodic (lower level) exposures to these and/or other co-occurring pollutants. Key studies and findings from such research on mortality associated with short-term exposures to particulate matter are evaluated in the following subsection. Section 12.6.2 contains later additional discussion on the validity of model specifications.

12.3.1 Mortality Effects Associated with Short-Term Particulate Matter Exposures

The National Center for Health Statistics (NCHS) mortality statistics used in most U.S. mortality studies were compiled in accordance with World Health Organization (WHO) regulations, which specify that member nations classify causes of death by the current Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death (World Health Organization, 1977). Causes of death for 1979 to 1991 were classified according to the ninth revision of the manual. For earlier years, causes of death were classified according to the revisions then in use—1968 through 1978, Eighth Revision; 1958 through 1967, Seventh

Revision; and 1949 through 1957, Sixth Revision. Changes in classification of causes of death due to these revisions may result in discontinuities in cause-of-death trends.

Mortality statistics are based on data coded by the States and provided to NCHS through the Vital Statistics Cooperative Program and from copies of the original death certificates received by the NCHS from the State Registration Offices. The National Center for Health Statistics (1993) reported that in 1991, in the United States, the death rate was 860.3 deaths per 100,000 population. In 1991 a total of 2,169,518 deaths occurred in the United States. The first three leading causes of death — diseases of the heart; malignant neoplasms; and cerebrovascular diseases — accounted for 64% of deaths. Chronic obstructive pulmonary disease and allied conditions surpassed accidents in 1991 as the fourth leading cause.

In 1991, life expectancy at birth reached a record high at 75.5 years. For those between 65 and 70 years of age, the average number of years of life remaining is 17.4 years. Women currently are expected to outlive men by an average of 6.9 years and white persons are expected to outlive black persons by an average 7.0 years. In 1991, the age-adjusted death rate for males of all races was 1.7 times that for females. In 1991, the age-adjusted death rate for the black population was 1.6 times that for the white population. The annual asthma death rate was consistently higher for blacks than for whites during the period 1980 through 1990; for blacks, the rate increased 52% (from 2.5 to 3.8 per 100,000), compared with a 45% increase (from 1.1 to 1.6 per 100,000) for whites (U.S. Centers for Disease Control, 1994). The National Center for Health Statistics (1994a) reported that, for January 1985 through December 1992, trends in mortality rates for diseases of the heart (including coronary heart disease) decreased. Mortality also showed a seasonal pattern, with death rates being higher in winter. Table 12-1 shows age specific and age-adjusted death rates for selected causes for 1979, 1990, 1991.

Samet et al. (1995) review deaths out of the hospital as a potentially sensitive indicator of a pollutant effect.

> "Clinical reports on case-fatality rates after patients are hospitalized for heart and lung disease support this emphasis on out-of-hospital deaths. Only a minority of persons hospitalized with heart and lung diseases die in the hospital, and life-support interventions probably alter the temporal relationship between an effect of pollution that leads to hospitalization and any eventual death. For example, in a recent U.S. study of community-acquired pneumonia (i.e., cases of pneumonia developing in persons living in the community), 16% of patients died in the hospital (Brancati et al., 1993). An even lower figure (4%) was reported from a study of community-acquired pneumonia in Sweden (Ortquist et al., 1990). Recent studies of myocardial infarction document a similar range

of survival rates during hospitalization (Jenkins et al., 1994; European Myocardial Infarction Project Group, 1993); even in patients with a prior myocardial infarction, mortality in the first 15 days following reinfarction was only 14% in a study in Israel (Moshkovitz et al., 1993). Surprisingly, only a minority of patients with COPD who are admitted with acute respiratory failure die while in the hospital, even though the condition of many patients is severe enough to warrant mechanical ventilation (Rieves et al., 1993; Weiss and Hudson, 1994). A pooled estimate from a recent series of patients hospitalized with COPD and acute respiratory failure showed an overall mortality rate of only 10% (Weiss and Hudson, 1994)."

12.3.1.1 Review of Short-Term Exposure Studies

The decade or so since the previous criteria document addendum was released (U.S. Environmental Protection Agency, 1986a) has been an active period for the reporting of time series analyses of associations between human mortality and acute exposures to PM (see Tables 12-2 and 12-3). In the beginning of this period, various PM measures of only

TABLE 12-1. AGE-SPECIFIC AND AGE-ADJUSTED UNITED STATES DEATH RATES FOR SELECTED CAUSES IN 1991 AND SELECTED COMPONENTS IN 1979, 1990, AND 1991 (Age-specific rates on an annual basis per 100,000 population in specified groups, age-adjusted per 100,000 U.S. standard million population)

Cause of death (Ninth Revision of International Classification of Diseases, 1975)	Year	Age: All ages[1]	Under 1 year[2]	1-4 years	45-54 years	55-64 years	65-74 years	75-84 years	85 years and over	Age-adjusted rate[3]
All causes	1991	860.3	916.6	47.4	468.8	1,181.0	2,618.5	5,890.0	15,107.6	513.7
	1990	863.8	971.9	46.8	473.4	1,196.9	2,648.6	6,007.2	15,327.4	520.2
	1979	852.2	1,332.9	64.2	589.7	1,338.0	2,929.0	6,496.6	14,962.4	577.0
Diseases of heart 390-398, 402, 404-429	1991	285.9	17.6	2.2	118.0	357.0	872.0	2,219.1	6,613.4	148.2
	1990	289.5	20.1	1.9	120.5	367.3	894.3	2,295.7	6,739.9	152.0
	1979	326.5	20.2	2.1	184.6	499.0	1,199.8	2,925.2	7,310.9	199.5
Hypertensive heart disease 402	1991	8.5	*	*	5.6	13.3	24.9	60.5	173.9	4.7
	1990	8.5	*	*	5.6	13.3	26.3	60.9	173.4	4.8
	1979	9.3	*	*	7.0	16.2	35.7	79.6	170.3	6.0
Ischemic heart disease 410-414	1991	192.5	0.5	*	75.5	240.5	605.8	1,536.7	4,374.1	99.1
	1990	196.7	0.7	*	77.7	248.6	627.0	1,602.5	4,498.1	102.6
	1979	245.5	0.7	*	136.1	381.0	926.6	2,224.8	5,376.1	149.7
Acute myocardial infarction 410	1991	93.3	*	*	45.0	138.2	326.3	752.9	1,669.4	51.5
	1990	96.1	*	*	46.5	144.3	342.1	793.6	1,695.5	53.7
	1979	133.8	*	*	94.6	258.9	577.2	1,135.2	1,916.3	88.2
Old myocardial infarction and other forms of chronic ischemic heart disease 412, 414	1991	97.5	*	*	29.2	99.4	273.9	772.2	2,671.5	46.6
	1990	98.8	*	*	29.7	101.3	279.0	796.7	2,769.4	47.8
	1979	109.4	*	*	39.3	117.0	340.3	1,072.2	3,424.9	59.9
Cerebrovascular diseases 430-438	1991	56.9	4.0	0.4	18.3	46.4	139.6	479.4	1,587.7	26.8
	1990	57.9	3.8	0.3	18.7	48.0	144.4	499.3	1,633.9	27.7
	1979	75.5	4.6	0.3	26.4	68.1	226.9	793.8	2,264.9	41.6
Chronic obstructive pulmonary diseases and allied conditions 490-496	1991	35.9	1.5	0.3	9.1	49.7	156.3	327.0	446.9	20.1
	1990	34.9	1.4	0.4	9.1	48.9	152.5	321.1	433.3	19.7
	1979	22.2	1.9	0.5	9.3	40.2	117.0	200.6	230.2	14.6
Pneumonia and influenza 480-487	1991	30.9	15.1	1.4	6.8	17.8	55.9	238.5	1,080.5	13.4
	1990	32.0	16.1	1.2	7.0	18.6	59.1	253.5	1,140.0	14.0
	1979	20.1	33.0	2.0	7.1	16.4	47.8	184.2	694.9	11.2

[1]Figures for age not stated are included in "All ages" but not distributed among age groups.
[2]Death rates under 1 year (based on population estimates) differ from infant mortality rates (based on live births).
[3]For method of computation, see technical notes in Source.

Source: National Center for Health Statistics (1993a).

*See technical notes in reference source.

TABLE 12-2. SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
KM (mean = 25; SD = 11)	Total, respiratory, and cardiovascular mortality in Los Angeles County (1970 to 1979) related to O_3, CO, SO_2, NO_2, HC, daily max. temp., RH, and KM (a PM metric of optical reflectance by particles, related to ambient carbon and fine particle concentration). Low pass filter used to eliminate short-wave, so that only long- wave associations studied.	Frequency domain analyses indicated stat. signif. ($p<0.05$) short- and long-wave associations with KM. The filtered (i.e., long-wave) data analysis also indicated that air pollution (including KM) was significantly associated with seasonal variations in LA mortality.	Shumway et al. (1988)
KM (mean = 25; SD = 11)	Los Angeles mortality (1970 to 1979) dataset of Shumway et al. (1988) analyzed using a high-pass filter to allow investigation of short-wave (acute) associations with environmental variables (by removing seasonality effects). Environmental variables considered in regression analyses included temp., RH, extinction coefficient, carbonaceous PM (KM), SO_2, NO_2, CO, and O_3.	Analyses showed stat. significant associations between short-term variations in total mortality and pollution, after controlling for temperature. Day-of-week effects did not to affect the relationships. Results demonstrated significant mortality associations with O_3 lagged 1 day, and with temp., NO_2, CO, and KM. Latter three pollutants highly correlated with each other, making it impossible to separately estimate PM associations with mortality.	Kinney and Ozkaynak (1991)
COH (monthly mean range = 9 to 12)	Daily total, respiratory, cancer, and circulatory mortality associations with daily COH in Santa Clara County, CA (1980 to 1982 and 1984 to 1986 winters). Daily mean temp. and RH at 4 p.m. also considered.	An association found between COH and increased mortality, even after adjustments for temperature, relative humidity, year, and seasonality.	Fairley (1990)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
BS (mean = 90.1 μg/m^3) (24-h avg. daily max. = 709 μg/m^3)	Daily total mortality analyzed for associations with BS, SO_2, and H_2SO_4 in London, England, during 1963 to 1972 winters. Mean daily temp. and RH also considered.	PM, SO_2, and H_2SO_4 all found to have stat. signif. associations with mortality (0, 1 day lag). Temp. also correlated (negatively) with mortality, but with 2-day lag. Seasonality addressed by studying only winters and by applying high-pass filter to the series and analyzing residuals.	Thurston et al. (1989)
BS (mean = 90.1 μg/m^3) (range = 0 to 350 μg/m^3)	Further analysis of London, England data (1965 to 1972) examined by Thurston et al. (1989). Spectral and advanced time series methods used, e.g. prewhitening and auto- regressive (AR) moving average (MA) methods. Variables considered included BS, SO_2, H_2SO_4, temp., and RH.	Estimated pollution mean effect of 2 to 7% of all London winter deaths (mean = 281/day), but various pollutants' effects not separated. Independent model test on 1962 episode confirmed appropriateness of such methods. Long-wave addressed by considering winters only and by prewhitening the data.	Ito et al. (1993)
Suspended Particles (SP) (range = 10 to 650 μg/m^3)	Daily total mortality in Erfurt, East Germany, during 1980 to 1989 (median = 6/day) related to SO_2, SP, T, RH, and precipitation. SP only measured 1988 to 1989. Autoregresssive Poisson models used (due to low deaths/day) also included indicator variables for extreme temp. and adjustments for trend, season, and influenza epidemics.	Both SO_2 and SP found to be significantly associated with increased mortality. In a simultaneous regression, SP remained significant while SO_2 did not. Correlations of these coefficients not provided, however. Pollution effect size similar to that for meteorology.	Spix et al. (1993)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
BS	Daily total mortality in Athens, Greece, and surrounding boroughs (1975 to 1987) related to BS, SO_2, NO_2, O_3, and CO_2 using multiple regression.	During winter months 1983 to 1987, the daily number of deaths was positively and statistically significantly associated with all pollutants, but the association was strongest with BS.	Katsouyanni et al. (1990a)
BS (annual mean range = 51.6 to 73.3 μg/m^3) (maximum daily value = 790 μg/m^3)	For 1975 to 1982 in Athens, Greece 199 days with high SO_2 (>150 μg/m^3) each matched on temp., year, season, day of week, and holidays with two low SO_2 days. Mortality by-cause compared between groups by ANOVA by randomized blocks. BS correlated with SO_2 at r = 0.73, but not directly used in analysis.	Mortality was generally higher on high SO_2 days, with the difference being most pronounced for respiratory conditions. BS levels for each group not provided, and BS-SO_2 confounding not addressed, limiting interpretability of results.	Katsouyanni et al. (1990b)
BS (range = 50 to 250 μg/m^3)	Daily total mortality in Athens, Greece, during July, 1987 (when a major heat wave occurred) compared to deaths in July for previous 6 yr. Variables considered included: BS, SO_2, temp., discomfort index (DI). Effects of day-of-week, month, and long-term trends addressed via dummy variables in OLS regression models.	Mean daily temperature above 30 °C found to be significantly associated with mortality. The main effects of all air pollutants nonsignificant, but the interaction between high air pollution and temp. significant for SO_2 and suggestive ($p < 0.20$) for ozone and BS.	Katsouyanni et al. (1993)
BS (mean = 83 μg/m^3) (range = 18 to 358 μg/m^3)	Daily total mortality in Athens, Greece, during 1984-1988 (mean = 38/day) related to BS, SO_2, CO, T, and RH. Autoregressive OLS models employed also included indicator variables for season, day of week, and year.	BS, SO_2, and CO each individually significantly associated with increased mortality. The size of all coefficients declined in simultaneous regressions, with SO_2 still significant and BS approaching significance. CO was no longer significant, but highly correlated with BS (r = 0.74).	Touloumi et al. (1994)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 87 μg/m^3) (24-h avg. range: 46 to 137 μg/m^3, 5th to 95th percentiles)	Total deaths in Detroit, MI (1973 to 1982) analyzed using Poisson methods. Variables considered included TSP, SO_2, O_3, temp., and dew point. Seasonality controlled via multiple dummy weather and time variables.	Signif. associations between mortality and TSP in autoregressive Poisson models (RR for 100 μg/m^3 TSP = 1.06). Most TSP data estimated from visibility, which is best correlated with fine particle portion of TSP. Thus, results suggest a fine particle association.	Schwartz (1991a)
TSP (mean = 77 μg/m^3) (max. = 380 μg/m^3) (5th to 95th percentiles = 37 to 132 μg/m^3)	Total and cause-specific daily mortality in Philadelphia, PA (1973 to 1980) related to daily TSP and SO_2 (n $\approx$2,700 days). No other pollutants considered in analysis. Poisson regression models, using GEE methods, included controls for year, season, temp., and RH. Autocorrelation addressed via autoregressive terms in model.	Strongest mortality associations with pollution on same and prior days. Total mortality (mean = 48/day) estimated to increase 7% (95% C.I. = 4 to 10%) for a 100 μg/m^3 increase in TSP. Larger cause-specific effects of TSP (as %). SO_2 associations non-significant in simultaneous models with TSP, but correlations of estimated coefficients not reported.	Schwartz and Dockery (1992a)
TSP (mean 65 range 14 to 338)	Reanalyses of Philadelphia mortality data, 1973-1988. Poisson regression models by season, adjusted for weather, year, SO_2, and O_3.	Relationship between TSP and mortality appears to be sensitive to inclusion of SO_2 or O_3, and differs by season.	Moolgavkar et al. (1995b)
TSP	Reanalyses of Philadelphia mortality data, 1973-1990, using filtered autoregressive regression models. Adjustments for weather, SO_2, O_3, and season, with particular attention to subset analyses for weather. Sensitivity analyses for lag structure.	TSP associated with mortality on hottest days, suggesting possible interaction. Little relationship of O_3 to mortality except on coldest days. Correlation structure suggests short-term mortality displacement.	Wyzga and Lipfert (1995b)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 69 $\mu g/m^3$) (5th to 95th percentiles = 32 to 120 $\mu g/m^3$)	Age and cause-specific daily mortality in Philadelphia, PA during 1973 and 1990 related to daily TSP, SO_2, and O_3. Other variables included were: temp., RH, barometric pressure, precipitation. Various models used, including poisson and autoregessive. Also applied prefiltering methods to remove long-waves.	TSP effect found only in winter. TSP never significant in by-cause analyses of those <15 or ≥65 years old. Addition of other pollutants (TSP-SO_2 r = 0.57) weakened TSP effects. Including barometric pressure and precipitation in the models may have acted as surrogates for PM, potentially confounding results. TSP correlations with other variables not given.	Li and Roth (1995)
TSP, Philadelphia (mean = 77.2, range = 22 to 338)	Reanalyses of 1973-1980 mortality in Philadelphia from Dockery and Schwartz (1992a), Moolgavkar et al. (1995a). Sensitivity analyses done for TSP and SO_2 relation to total mortality and for elderly and non-elderly mortality, including adjustments for season, weather, time trend, lags, and moving averages. Analyses also for total cardiovascular mortality, pneumonia and emphysema mortality, cancer mortality. Poisson regression and various autoregressive models compared. Nonparametric LOESS models for mortality vs. TSP and SO_2 developed. Quantile models assessed for TSP, SO_2, weather.	Control for weather variables had little effect on results. Both TSP and SO_2 had effects on mortality, but TSP had little effect unless TSP > 100 $\mu g/m^3$, whereas SO_2 had a positive effect on mortality at lower concentrations, but showed little relation at higher concentrations. Seasonal effects important, with TSP dominant in summer and SO_2 in winter. Lag structures analyses confirmed earlier findings of greater effect from more recent exposures.	Samet et al. (1995)
TSP	Reanalyses of 1973-1980 Philadelphia mortality data with emphasis on model specification for weather variables. Additive Poisson regression models fitted to TSP and SO_2, adjusting for time trend and weather. The weather adjustments tested were of original investigators (Schwartz and Dockery, 1992a) and two different synoptic weather categories. Both nonparametric regressions and LOESS used.	The associations of mortality to TSP and SO_2, alone or together not attributable to differences in the weather model. Models that can be adjusted to fit the mortality data provides a better fit than objective weather models not adjusted to mortality. Little evidence that weather categories modified the TSP effect.	Samet et al. (1996b)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 37 $\mu g/m^3$) range = 14 to 222	Reanalyses of 1974-1988 Philadelphia mortality data with emphasis on copollutants. Additive linear Poisson regression models fitted with TSP, SO_2, NO_2, and O_3, over same plus preceding day, as well as lagged CO(LCO) averaged over 3- and 4-day lags. All pairs of pollutants tested as well as models with 5 or 6 pollutants. Models adjusted for weather, time, season, and day of week.	O_3 and LCO has significant positive effects on mortality not confounded with other pollutants. TSP and SO_2 not sig. when both in models, but had larger and more sig. effects when other pollutants included. Seasonality important, with TSP larger effect in spring and summer and O_3 in fall and winter. NO_2 had no sig. effect unless TSP and SO_2 in model. CO never had significant effect.	Samet et al. (1996a)
TSP	Reanalyses of 1983-1988 total mortality data for Philadelphia, by sex, race, age, and place of death. Poisson regression models adjusted for weather and time were fitted to additive linear models including SO_2 and O_3. Sensitivity to TSP model specification was tested using liner and piecewise linear models and quintile models for TSP. Lagtime and moving average models were compared. Mortality displacement was assessed by comparing mortality residuals and episodes.	A positive and significant TSP effect found, while O_3 was marginally significant and SO_2 not significant. The TSP effect was similar when data divided by sex, race, age group, and place of death. There appeared to be a smaller TSP effect at concentrations below about 60 to 90 $\mu g/m^3$ than at concentrations above 100 $\mu g/m^3$. A substantial number of the excess deaths during TSP episodes appeared to be a few days premature.	Cifuentes and Lave (1996)
TSP (mean = 111 $\mu g/m^3$) (24-h avg. range: 36 to 209 $\mu g/m^3$, 10th to 90th percentiles)	Daily total mortality in Steubenville, OH (1974 to 1984) related to TSP, SO_2, temp., and dew point. Poisson regression used, because of very low death counts/day (mean = 3.1). Regressions controlled for season by including dummy variables for winter and spring, and autoregressive methods used to address any remaining autocorrelation.	In regressions controlling for season and weather, previous day's TSP was significant predictor of daily mortality. SO_2 was less significant in regressions, becoming nonsignificant when entered simultaneous with TSP. Auto-regressive models gave similar results.	Schwartz and Dockery (1992b)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure x(Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 113 $\mu g/m^3$) (10th to 90th percentiles = 38 to 212 $\mu g/m^3$)	Daily mortality in Steubenville, OH (1974 to 1984) related to TSP, SO_2, temp., and dew point (to allow comparisons of results with Schwartz and Dockery, 1992b). Poisson method used; analyses done overall and by-season at same time period and location as in Schwartz and Dockery (1992b).	In single pollutant models, TSP coefficient was same as in Schwartz and Dockery (1992b), but TSP effects attenuated by SO_2 inclusion in the model. SO_2 also attenuated by addition of TSP. Concluded that TSP and SO_2 effects cannot be separated in this dataset. Intercorrelations among these variables not presented.	Moolgavkar et al. (1995a)
TSP (mean = 52 $\mu g/m^3$; SD = 19.6 $\mu g/m^3$)	Daily total and cause-specific mortality in Cinci., OH (mean total = 21/day) during 1977 to 1982 related to TSP, temp., dew point. Poisson model used with dummy variables for each month and for eight (unspecified) categories of temp. and dew point. Linear and quadratic time trend terms also included, spline and nonparametric models applied. Autocorrelation not directly addressed.	TSP significantly associated with increased risk of total mortality. Relative risk higher for elderly and for those dying of pneumonia and cardiovascular disease. However, the analysis did not consider other pollutants, and there remains the potential for within-month, long-wave confoundings.	Schwartz (1994a)
TSP (OECD Method) (Lyons, France: 3 year mean = 87 $\mu g/m^3$) (Marseilles, France 3 y mean = 126 $\mu g/m^3$)	Daily total, respiratory, and cardiac mortality for persons $\geq$65 years of age tested for associations with SO_2 and TSP during 1974 to 1976 in Lyons and Marseilles, France. Temperature also considered in analyses.	No sig. mortality associations found with TSP, but SO_2 reported as associated with total elderly deaths in both cities. Seasonality addressed by analyzing deviations from 3-year average of 31-day running means of variables, but temp. lags not considered and probable seasonal differences in winter/summer temp.-mortality relationship not addressed.	Derriennic et al. (1989)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
TSP (mean = 375 μg/m^3) (maximum = 1,003 μg/m^3)	Daily deaths during 1989 in two residential areas in Beijing, China (mean total deaths = 21.6/day) related to TSP and SO_2 using Poisson methods. Controlling for other variables included quintiles of temp. and humidity. Long-wave confounding and autocorrelation not directly addressed, but season-specific results presented.	Sig. mortality associations for ln (SO_2) and ln (TSP). Associations strongest for chronic respiratory diseases. In simultaneous regressions, SO_2 sig., but not TSP. However, the two pollutants highly correlated with each other (r = 0.6), as well as with temp.; in season-specific analyses, both were sig. in summer, but only SO_2 in winter.	Xu et al. (1994)
PM_{10} (mean = 47 μg/m^3) (24 h max. = 365 μg/m^3) (5 day max. = 297 μg/m^3)	Total, respiratory, and cardiovascular mortality in Utah County, UT (1985 to 1989) related to 5-day moving average PM_{10}, temp., and RH. Time trend and random year terms also included in autoregressive Poisson models. Seasonality not directly addressed in basic model, but addition of four seasonal dummy variables changed results little.	Significant positive association between total non-accidental mortality. Strongest association with the 5-day moving average of PM_{10}. Association largest for respiratory disease, next largest for cardiovascular, and lowest for all other. Association seen below 150 μg/m^3 PM_{10}. Possible influences of other pollutants discussed, but not directly addressed.	Pope et al. (1992)
PM_{10} (mean = 47 μg/m^3) (range = 1-365 μg/m^3)	Reanalyses of Utah Valley mortality date for 1985-1989 with emphasis on alternative model specifications for weather. Poisson regression models fitted to all cause, pulmonary, and cardiovascular mortality, using moving averages of PM_{10} up to 5 days after adjustment for time trend and weather. Sensitivity to weather adjustments tested by comparing LOESS models, 19 synoptic weather categories, and quintile indicators. Models with hot/cold season also tested. Both linear and LOESS models for PM_{10} used.	The estimated PM_{10}-mortality relationship remained positive, significant, and only moderately sensitive to any of the alternative model specifications for weather. The relative risk was somewhat larger for cardiovascular mortality, but much higher for pulmonary mortality. Longer PM_{10} averaging times (4-6 days) provided best fit to mortality from all causes.	Pope and Kalkstein (1996)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} St. Louis, MO: (mean = 28 μg/m^3) (24 h max. = 97 μg/m^3) Kingston/Harriman, TN (mean = 30 μg/m^3) (24 h max. = 67 μg/m^3)	Total mortality in St. Louis, MO and Kingston/Harriman, TN plus surrounding counties (September 1985 to August 1986) related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, H^+, temp., dew point, and season using auto-regressive Poisson models.	In St. Louis, statistically significant daily mortality associations with PM_{10} and $PM_{2.5}$, but not other pollutants. In Kingston/Harriman, PM_{10} and $PM_{2.5}$ approached significance, but not other pollutants. Seasonality reduced by season indicator variables, but within season long wave cycles not directly addressed.	Dockery et al. (1992)
PM_{10} (mean = 48 μg/m^3) (24 h max. = 163 μg/m^3)	Total daily mortality in Birmingham, AL (from August 1985 to December 1988) related to PM_{10}, temp, dew point. Poisson models used addressed seasonal long wave effects by including 24 sine and cosine terms having periods of 1 mo to 2 years. Autoregressive linear models also applied.	Significant associations between total mortality and prior day's PM_{10}. Various models gave similar results, as did eliminating all days with PM_{10} >150 μg/m^3. However, possible roles of other pollutants not evaluated.	Schwartz (1993a)
PM_{10} (mean = 40 μg/m^3) (24 h max. = 96 μg/m^3)	Total, cardiovascular, cancer, and respiratory mortality in Toronto, Canada (during 1972 to 1990) related to PM_{10}, TSP, SO_4, CO, O_3, temp., and RH. Moving average (19-day) filtered data used in OLS regressions. Using model developed from 200 PM_{10} sampling days during the period, 6303 PM_{10} values estimated based on TSP, SO_4, COH, visibility (B_{ext}) and temp. data.	Significant associations between mortality and all pollutants considered, after controlling for weather and long wave influences. However, not possible to separate PM_{10} association from other PM measures. Simultaneous PM and ozone regressions gave significant coefficients for each, but intercorrelations among pollutants not presented.	Ozkaynak et al. (1994)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (mean = 58 μg/m^3) (24 h max. = 177 μg/m^3)	Total mortality in Los Angeles, CA (during 1985 to 1990) related to PM_{10}, O_3, CO, temp., and RH. Poisson models used addressed seasonal long-wave influences by including multiple sine and cosine terms of 1 mo to 2 years in periodicity. OLS and log linear models also tested. Winter and summer also analyzed separately.	PM_{10} and mortality associations only mildly sensitive to modeling method. CO also individually significant. Addition of either CO or O_3 lowered significance of PM_{10} in model somewhat, but PM_{10} coefficient not as affected, indicating minimal effects on PM_{10} association by other pollutants in this case.	Kinney et al. (1995)
PM_{10} (mean = 38 μg/m^3) (24 h max. = 128 μg/m^3)	Total mortality in Los Angeles, CA and Chicago, IL during 1985 through 1990 related to PM_{10}, O_3, and temperature. Analysis focused on importance of monitor choice to modeling results. Poisson models used addressed seasonal long wave influences by including multiple sine/cosine terms ranging from 1 mo to 2 years in periodicity.	Average of multiple sites' PM_{10} significantly associated with mortality in each city after controlling for season, temperature and ozone. Other pollutants and relative humidity not yet considered. Individual sites' PM_{10} varied from non-significant to strongly significant. Also, dividing the data by season diminished the significance of the multi-site average PM_{10} in mortality regressions. Both site selection and sample size concluded to influence results.	Ito et al. (1995)
PM_{10} (mean = 115 μg/m^3) (24 h max. 367 μg/m_3)	Total, respiratory, and cardiovascular daily deaths/day (means = 55, 8, and 18, respectively) in Santiago, Chile during 1989 through 1991 related to PM_{10}, O_3, SO_2, NO_2, temperature and humidity. Seasonal influences addressed by various methods, including seasonal stratification, the inclusion of sine/cosine terms for 2.4, 3, 4, 6, and 12 month periodicities, prefiltering, and the use of a nonparametric fit of temperature. Log of PM_{10} modeled using OLS with first order autoregressive terms.	Significant association found between PM_{10} and daily mortality, even after addressing potential confounders (e.g., weather), other pollutants, lag structure, and outliers. Strongest associations found for respiratory deaths. SO_2 and NO_2 each also significantly associated, but only PM_{10} remained significant when all added simultaneously to the regression. Correlations of the coefficients not reported.	Ostro et al. (1996)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (mean = 82.4 $\mu g/m^3$) (24 h avg. SE = 38.9 $\mu g/m^3$)	Respiratory mortality among children < 5 years old (mean = 3/day) in Sao Paulo, Brazil during May 1990 through April 1991 related to PM_{10}, SO_2, NO_x, O_3, CO, temperature, humidity, and day of week. Season addressed by including seasonal and monthly dummy variables in regressions. Mortality data adjusted for non-normality via a square root transformation.	Significant association found between respiratory deaths and NO_x, but no other pollutants. No such association found for non-respiratory deaths. However, auto-correlation not addressed. Also, inter-correlations of the pollutant coefficients not reported (but NO_x - PM_{10} correlation = 0.68)	Saldiva et al. (1994)
PM_{10} (mean = 82.4 $\mu g/m^3$) (24 h avg. SE = 38.9 $\mu g/m^3$)	Total mortality among the elderly ($\geq$ 65 years old) (mean = 63/day) in Sao Paulo, Brazil during May 1990 through April 1991 related to two day avg. of PM_{10}, SO_2, NO_x, O_3, and CO, and to temperature, humidity, and day of week. Season addressed by including seasonal and monthly dummy variables. Temperature addressed using three discrete dummy variables.	Significant associations found between total elderly deaths and all pollutants considered. In a simultaneous regression, PM_{10} was the only pollutant which remained significant. The PM_{10} coefficient actually increased in this regression, suggesting interpollutant interactions. Correlations of the pollutant coefficients not provided.	Saldiva et al. (1995)
PM_{10} (Cook County median = 37 $\mu g/m^3$; max = 365 $\mu g/m^3$) (Salt Lake County median = 35 $\mu g/m^3$; max = 487 $\mu g/m^3$)	Total, respiratory, circulatory, and cancer mortality in Cook County (1985 to 1990). Elderly, total by race and sex also evaluated. Poisson regression with seasonal adjustments, meteorological variables, and pollen tested. In Salt Lake County, total and elderly mortality. One daily station in Cook County and two daily monitoring stations in Salt Lake County, plus multiple every 6th-day stations.	Average and single site PM_{10} were significant predictors in Cook County for total, elderly, cancer, and elderly white mortality, marginal for respiratory, circulatory, and elderly black. Significant Fall and Spring mortality in Cook County, not Summer or Winter. No significant effects in Salt Lake County. No copollutants.	Styer et al. (1995)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10} (variable by month and year)	Reanalysis of Utah County mortality (1985 to 1992), broken down by year, season, cause and place of death. PM_{10} entered as dichotomous variable (less or greater than 50 $\mu g/m^3$). No adjustment for copollutants or weather in Poisson regression, except for daily minimum temp. Poisson regression, not GEE.	Variations in RR did not appear to be associated with high or low PM_{10} days. High RR for cancer deaths (age < 60) at home. Highest RR in spring. Also, increased RR for sudden infant death syndrome.	Lyon et al. (1995)
PM_{10} (mean 41 ± 19 $\mu g/m^3$)	Total deaths, circulatory, cancer, respiratory, and other deaths in Cook County, IL for 1985-90 were related to PM_{10} other pollutants using Poisson regression models adjusted for weather season, time trend, and day of week. Analyses were carried out for race and gender.	Significant positive associations were found between PM_{10} and total mortality similar to other studies. Higher sig. effects were found for respiratory and for cancer mortality, while circulatory deaths showed a small positive non-sig. association. Other causes showed no relationship. African-American females showed a significantly higher risk for total mortality.	Ito and Thurston, (1996)

TABLE 12-2 (cont'd). SUMMARIES OF RECENTLY PUBLISHED EPIDEMIOLOGICAL STUDIES RELATING HUMAN MORTALITY TO AMBIENT LEVELS OF PARTICULATE MATTER

PM Measure (Concentrations)	Study Description	Results and Comments	Reference
PM_{10}: Portage, WI 18 ± 12 $\mu g/m^3$ Boston, MA 24 ± 13 $\mu g/m^3$ Topeka, KS 27 ± 16 $\mu g/m^3$ St. Louis, MO 31 ± 16 $\mu g/m^3$ Knoxville, TN 32 ± 15 $\mu g/m^3$ Steubenville, OH 46 ± 32 $\mu g/m^3$ $PM_{2.5}$: Portage, WI 11 ± 8 $\mu g/m^3$ Boston, MA 16 ± 9 $\mu g/m^3$ Topeka, KS 12 ± 7 $\mu g/m^3$ St. Louis, MO 19 ± 10 $\mu g/m^3$ Knoxville, TN 21 ± 10 $\mu g/m^3$ Steubenville, OH 30 ± 22 $\mu g/m^3$	Total COPD, IHD, pneumonia, and elderly mortality in six cities from 1979 to 1988 related separately to every-other-day. $PM_{10/15}$, $PM_{2.5}$, CP = $PM_{(15-2.5)}$, $SO_4^=$, and H^+, after adjustment for temp., dewpoint, time trend, indicators for rain, snow, day of week. Combined analyses for both $PM_{2.5}$ and CP. Poisson regressions linear in PM index, with nonparametric fits for weather and time. Lag structure not investigated. Variance-weighted combined estimates. Sensitivity analyses for weather control, nonlinear effect of $PM_{2.5}$.	Significant positive relationships for total mortality vs $PM_{2.5}$ in three cities, positive but less significant in others. Significant positive relationships for total mortality vs PM_{10} in four cities, positive but weather in Portage, negative but not sig. in Topeka. No significant relationship between CP and mortality except in Steubenville. Combined analyses sig. and positive for all causes, with larger effects in elderly and for IHD, COPD, and pneumonia. Smaller sig. relationship of mortality to $SO_4^=$, relationship to H^+ was small non-sig. No analyses of copollutants.	Schwartz et al., (1996a)

TABLE 12-3. INTERCOMPARISONS OF PUBLISHED PARTICULATE MATTER-ACUTE MORTALITY STUDY RESULTS BASED ON CONVERSION OF VARIOUS PARTICULATE MATTER MEASURES TO EQUIVALENT PM_{10} ESTIMATES

Health Outcome	Synthesis Study	Location	Original PM Measurement	Mean Equivalent PM_{10}	Percent Change Per 10 $\mu g/m^3$ PM_{10} Equivalent	95 Percent Confidence Interval
Total Mortality	Ostro (1993)	London UK	BS	80	0.3	(0.29, 0.31)
		Steubenville OH	TSP	61	0.6	(0.44, 0.84)
		Philadelphia PA	TSP	42	1.2	(0.96, 1.44)
		Santa Clara CA	COH	37	1.1	(0.73, 1.51)
	Dockery and Pope (1994b)	St. Louis MO	PM_{10}	28	1.5	(0.1, 2.9)
		Kingston TN	PM_{10}	30	1.6	(-1.3, 4.6)
		Birmingham AL	PM_{10} (3d)[1]	48	1.0	(0.2, 1.5)
		Utah Valley UT	PM_{10} (5d)[2]	47	1.5	(0.9, 2.1)
		Philadelphia PA	TSP (2d)[3]	40	1.2	(0.7, 1.7)
		Detroit MI	TSP	48	1.0	(0.5, 1.6)
		Steubenville OH	TSP	61	0.7	(0.4, 1.0)
		Santa Clara CA	COH	35	0.8	(0.2, 1.5)
Respiratory Mortality	Dockery and Pope (1994b)	Birmingham AL	PM_{10} (3d)	48	1.5	(-5.8, 9.4)
		Utah Valley UT	PM_{10} (5d)	47	3.7	(0.7, 6.7)
		Philadelphia PA	TSP (2d)	40	3.3	(0.1, 6.6)
		Santa Clara CA	COH	35	3.5	(1.5, 5.6)
Cardiovascular Mortality	Dockery and Pope (1994b)	Birmingham AL	PM_{10} (3d)	48	1.6	(-1.5, 3.7)
		Utah Valley UT	PM_{10} (5d)	47	1.8	(0.4, 3.3)
		Philadelphia PA	TSP (2d)	40	1.7	(1.0, 2.4)
		Santa Clara CA	COH	35	0.8	(0.1, 1.6)

[1]Three day moving average.
[2]Five day moving average.
[3]Two day moving average.

indirect applicability to the standard setting process (e.g., TSP, BS, KM, or COH) were usually employed. However, in the last few years the analyses have more often employed PM_{10} as a measure of PM. This is because sufficient routine PM_{10} ambient measurement data began to be available for such statistical analyses to be conducted in a wide variety of locales. The focus of this section is on detailed assessments of those studies conducted since the PM criteria document addendum (U.S. Environmental Protection Agency, 1986a). Of special interest are studies that have employed PM_{10} in their analyses of the human mortality effects of acute exposures to PM; although studies employing other indices of PM exposures are summarized in tables and discussed in the text, as appropriate.

As shown in Table 12-2, a variety of PM metrics have been employed in time-series studies relating PM to acute mortality. These have included gravimetric measures, such as total suspended particulate matter (TSP) and PM_{10}, the former of which measures a significant portion of extrathoracic particles. In addition, many studies have employed data from various samplers that yield BS or KM optical measurements of particle reflectance of light, or coefficient of haze (COH) optical measurements of particle transmission of light. All of these latter metrics (BS, KM, COH) are most directly related to ambient elemental carbon concentration (e.g., see Bailey and Clayton, 1982; Wolff et al., 1983; Cass et al., 1984), but only indirectly related to particle (most closely fine particle) mass, as the relationship with mass will vary as sampled particle size, shape, color, and surface characteristics vary over time and between sites. Hence, unless side-by-side calibrations of these optical measurements are made against direct mass measurements obtained by collocated gravimetric monitoring instruments, such optical measurements cannot be readily converted to quantitative estimates of ambient PM mass concentrations or associated PM-mortality relationships. Thus, given the diversity of nonequivalent PM metrics employed across many of the reviewed epidemiology studies, attempting quantitative intercomparisons between results of all of the various reviewed epidemiologic studies necessarily introduces additional uncertainties, although attempts have been made by using conversion factors (Schwartz, 1992a; Ostro, 1993; Dockery and Pope, 1994b; Lipfert and Wyzga, 1995a; Pope et al., 1995a). Lipfert and Wyzga (1995a,b) report results in terms of elasticities, which do not require conversion factors.

The two studies using KM as the PM metric employed very different approaches to the same data set from Los Angeles during 1970 to 1979. The study by Shumway et al. (1988)

evaluated long-wave associations and found significant KM-mortality associations, but this analysis did not assess for seasonal effects. The KM study by Kinney and Ozkaynak (1991) more appropriately studied the short-wave associations of multiple pollutants, finding KM to be significantly associated with total mortality, but collinearities among KM, NO_2, and CO made it "impossible to uniquely estimate their separate relationships to mortality."

Similar to the KM studies, BS studies are quite varied in approach. Thurston et al. (1989) applied a high pass filter (similar to that employed by Kinney and Ozkaynak, 1991) to the 1963 to 1972 London, England wintertime mortality-pollution data set, whereas Ito et al. (1993) analyzed a subset of the same data using prewhitening and autoregressive techniques. In both, BS, SO_2, and H_2SO_4 were all found to be significantly associated with mortality, but the effects of each were not separable due to the high collinearity among these pollution metrics. Katsouyanni et al. (1990a) similarly found an association between total mortality and all pollutants measured in Athens, Greece during 1975 to 1987, although they reported BS to be most strongly associated. A separate randomized block analysis of SO_2 and by-cause mortality during this same period (Katsouyanni et al., 1990b) found significant SO_2 effects, but SO_2 and BS were correlated at $r = 0.73$. A subsequent analysis by Katsouyanni et al. (1993) of summer heat wave periods found a significant temperature-SO_2 interaction term, and the suggestion of an interaction ($p < 0.2$) for BS.

A study using BS as the PM index which carefully addressed potential confounding effects of other pollutants and temperature was conducted by Touloumi et al. (1994) for daily all-cause mortality in Athens, Greece during 1984 through 1988. In this study, BS (mean = 83 $\mu g/m^3$), SO_2 (mean = 45 $\mu g/m^3$), CO (mean = 6 $\mu g/m^3$), temperature, and relative humidity were all modeled separately and simultaneously, giving a range of estimates for PM effects, depending on the model specification. The five years of data employed provided ample numbers of records for the analysis (e.g., $n = 1684$ for BS). Temperature associations were simply but effectively modeled. The authors examined the bivariate temperature-mortality plot and noted a mortality minimum around 23 °C daily mean temperature. They then defined two temperature variables: one as the daily mean temperature deviation below 23 °C; the other as the daily deviation above 23 °C (whichever was relevant), thereby allowing a separate modeling of the cold and hot weather effects on mortality. The square of each of these (lagged one day) gave the best fit of the mortality, and these terms were used in subsequent pollutant models. Multiple

monitoring stations were averaged (e.g., 5 for BS) after filling in missing observations from available data on the same day at other sites, providing spatially representative exposure estimates. Ordinary least squares modeling was applied, which is acceptable in this case given the relatively large number of mortality counts/day (mean = 38 deaths/day, SE = 12) in this metropolitan area. Day-of-week, season, hot (> 23 °C) and cold (<23 °C) temperature deviations squared, and relative humidity terms were also included in mortality regressions on pollutants. Although the use of only a dummy term for each season could not have fully addressed the within-season long wave mortality trends shown in time series plots, autoregressive modeling did address any resulting residual autocorrelation. Also, use of a single annual sine curve with periodicity of 1 year (phase not reported) gave similar results.

Separating the effects of the various air pollutants was attempted in this analysis of Athens mortality, but proved challenging. The log of pollutant concentrations were entered into the basic model both individually and simultaneously. All pollutants considered were individually significant at the $p = 0.0001$ level. When copollutants were simultaneously entered, SO_2 was the least affected, both in terms of coefficient size and statistical significance. The BS coefficient dropped in size by 50% when entered with SO_2 in the model, and its statistical significance weakened (as expected when correlated variables are entered together) but remained significant ($p = 0.02$, two-tailed test). However, SO_2 declined by less than 30 percent and remained significant at the $p = 0.002$ level in simultaneous regressions. The CO coefficient decreased in size by 75% and became clearly non-significant when entered with either SO_2 or BS. The authors noted, however, that these pollutants are highly intercorrelated over time (e.g., for CO and BS, $r = 0.79$). Thus, while the most consistent mortality association, both in terms of size and significance of its coefficient, appears to be with SO_2 in this city, the colinearities among these primary, combustion-related, air pollutants precludes quantitative apportionment of effects to individual pollutants. The authors acknowledged this, concluding that relatively low-level air pollution has a small but real effect on mortality. Using BS alone as the index of ambient air pollution, the authors reported that a 10% decrease in BS to be associated with a 0.75% decrease in total mortality. Using an on-site calibration with PM_{10} ($PM_{10} = 8.70 + 0.832 \times BS$) developed for this city (Katsouyanni, 1995) yields a mean PM_{10} of 77.7 $\mu g/m^3$ and a relative risk (RR) of 1.07 for a 100 $\mu g/m^3$ increase in PM_{10} (i.e., to 203 $\mu g/m^3$ BS). However, when the BS coefficient from the simultaneous regression with other pollutants is used, the estimated RR per

100 $\mu g/m^3$ increase in PM_{10} drops to 1.03. Thus, the estimate of the total mortality RR of a one day 100 $\mu g/m^3$ increase in PM_{10} implied by this work ranges from 1.07 to 1.03, depending on whether the PM metric is entered into the regression singly or in combination with other pollutants, respectively.

Recent Studies Using TSP

Studies evaluating TSP effects have also yielded mixed results as to the relative role of PM, versus other pollutants, in mortality. For example, Schwartz (1991a) examined total mortality in Detroit during 1973 to 1982, finding TSP to be more strongly associated with mortality than SO_2. However, the correlation between SO_2 and TSP was not reported, other pollutants likely to have been present (e.g., CO and NO_2) were not considered in the analysis, and most of the TSP values were estimated from visibility records, which are most strongly correlated with fine particles (e.g., see Ozkaynak et al., 1986). The Schwartz and Dockery (1992b) analysis of 1974 to 1984 mortality in Steubenville, OH similarly concluded that TSP was more significant than SO_2, but neither considered other pollutants nor reported the correlation between SO_2 and TSP in this valley locale. A Schwartz (1994a) analysis of Cincinnati, OH, mortality during 1977 to 1982 also found a TSP-mortality association, but did not consider other pollutants. Derriennic et al. (1989) examined mortality among the elderly in two French cities during 1974 to 1976 and found mortality associations with SO_2, but not with TSP (although the model specification for temperature did not address possible lag structure or season). Spix et al. (1993) found significant suspended particle (SP)[1] and SO_2 associations with mortality in Erfurt, East Germany, during 1980 to 1989, with SP remaining significant in simultaneous regressions, despite very high SO_2 levels. Xu et al. (1994) also reported significant mortality associations with SO_2 and TSP (other pollutants not considered) in Bejing, China, but found that SO_2 (not TSP) remained significant in simultaneous regressions.

TSP Studies of Philadelphia

Schwartz and Dockery (1992b) also found a TSP effect in Philadelphia. Subsequent reanalyses of these data have become the primary basis for comparing different modeling

[1]It is not clear as to how the reported SP results might best relate to one or another of other PM indicators, e.g., BS, TSP, PM_{10}, $PM_{2.5}$, etc.

strategies (Wyzga and Lipfert, 1995b; Li and Roth, 1995; Moolgavkar et al., 1995b; Cifuentes and Lave, 1996; Samet et al., 1995).

One reanalysis of the Philadelphia TSP data was reported by Moolgavkar et al. (1995b). This analysis used 1973 to 1988 data on TSP, SO_2, and ozone, with seasons defined by month (December to February for winter, March to May for spring, June to August for summer), and omitting January to February 1973 due to many missing values. The paper reported mortality quintiles and air pollution quintiles by season, combined over all years even though levels changed substantially during the 16-year interval analyzed in the study. The analyses were performed using Poisson regression fitted by GEE methods. The analyses rejected the hypothesis of common temperature and pollution effects in all years and seasons, but not the "Basic" model which used a different intercept for each year with common temperature and pollution effects.

The authors found substantial seasonal differences in air pollution effects on mortality. In summer, there was a statistically significant TSP effect that was little affected by including SO_2 in the model, but reduced to marginal significance by including O_3. In fall and in spring, there was a significant TSP effect that was reduced to non-significance by including SO_2, but actually increased when O_3 was included in the model. In winter, there was a significant TSP effect, but the effect disappeared when SO_2 (which was highest during winter) was included in the model, but little affected by including low winter O3 levels in the model. The RR for 100 $\mu g/m^3$ was about 1.05 in each season when TSP was the only pollutant in the model. This analysis is discussed in more detail in Section 12.6.

Another recent analysis of Philadelphia TSP data has been presented by Cifuentes and Lave (1996). These authors used the more recent time series from 1983 through 1988. The relationship between mortality and air pollution was explored for sensitivity to co-pollutants and weather variables, season, age group, and place of death. These analyses were particularly noteworthy because they also explored nonlinearities in the concentration-response function that could be characterized by piecewise linear models. The models were not, however, "threshold" models in the strictest sense. There were also extensive explorations of the prematurity of death for the periods of time of a few days accessible to daily time series data.

Cifuentes and Lave (1996) used log-linear and Poisson regression models. Time series correlation structure was not specified, except to note that missing values in the air pollution

records were imputed by predictions from a regression model. The air pollutants of interest were TSP, SO_2, and O_3. The mortality regression model predictors considered included the daily averages of the three pollutants or daily maximum hourly values of SO_2 or O_3 across several monitors in Philadelphia county. For TSP, monitor 03 was more predictive than monitor 04 or the average across all monitors, and same day or 1-day lag moving averages were most predictive. For SO_2, the same-day daily average was more predictive than the daily maximum or lagged values. For O_3, the average of the daily maxima of the current and previous day was most predictive. The air pollution concentration metric that best predicted mortality was used for each pollutant. The authors found that TSP was statistically significant even when all three pollutants were included in the model. The SO_2 coefficient was significant alone, but decreased markedly when TSP was included in the model. O_3 was marginally significant even when all three pollutants were included. The results were relatively insensitive to specification of the weather model.

Just as in Moolgavkar et al. (1995b), Cifuentes and Lave (1996) found that there were some important seasonal differences. During winter, TSP was less significant than SO_2, and when both pollutants were included in the model, neither was significant, which may reflect the relatively higher correlation between TSP and SO_2 during these Philadelphia winters. However, the TSP coefficient was relatively stable across the other seasons, and significant in spring and summer, whereas SO_2 was significant only in winter and only without TSP in the model.

As noted in Section 12.2, there are several possible concentration-response function specifications that allow evaluation of possible threshold or break point values. One method is to test if the regression coefficients are not significantly different when the data are broken into two separate parts at a specified cutpoint concentration. A second approach combines both fractions of the split data and assumes that there is a linear relationship with a possibly different regression coefficient in each segment. There appear to be different regression regimes for data split at TSP concentrations of about 90 to 100 $\mu g/m^3$. However, the regression coefficient at concentrations less than about 50 to 60 $\mu g/m^3$ may be larger than the coefficient for higher concentrations, which is the opposite of a "threshold" effect, although the coefficients are poorly estimated with this reduced range of concentrations and smaller number of daily observations. These analyses suggest that the actual relationship may be more complicated than a simple

piecewise linear model, possibly due to a more complex nonlinear relationship involving copollutants or other covariates.

The potential for mortality displacement (harvesting) was examined in different ways. One method was to look at mortality autocorrelation coefficients. Total mortality showed a negative correlation at lag 2 days, and "deaths outside of hospital" inpatients had negative autocorrelation for lags 1 and 2 days. This is consistent with depletion of a potentially susceptible population by acceleration of death by 1 or 2 days, but is not a strong demonstration of the hypothesis.

A much more detailed analysis was based on the definition of "episodes" by Cifuentes and Lave (1996). Episodes are contiguous periods of time in which pollution levels tend to be relatively elevated. They identified more than 100 such 3-day "episodes" during the 6 year period. Positive residuals (excess mortality) during the episode and negative residuals after the episode suggest displacement of mortality during that episode. The authors estimate that from 37% to 87% of the adult deaths that occur during the episode may have been displaced by a few days as a result relative to the pollution exposure episode, and that alternative explanations such as unusual weather events cannot account for the mortality deviations observed during that period of time. This hypothesis and the analytical methods used to test the hypothesis require further study.

Health Effects Institute Analyses (Samet et al., 1995)

An extensive series of reanalyses of air pollution mortality data has been carried out by Samet et al. (1995) as part of the Health Effects Institute study on particulate matter and health. These reanalyses involved reconstruction of databases using data provided by several investigators (D. Dockery, D. Fairley, S. Moolgavkar, A. Pope, J. Schwartz) that would allow evaluation of their published daily time series analyses for Philadelphia, St. Louis, Eastern Tennessee (Harriman-Kingston), Utah Valley, Birmingham, and Santa Clara. A number of new statistical methods were developed for fitting Poisson time series regression models using Generalized Estimating Equation (GEE) techniques. The purposes of the reanalyses of Philadelphia data for 1973 to 1980 included testing the sensitivity of the results to alternative model specifications for temperature and dewpoint, for TSP and SO_2 (singly and jointly), and for effects of season, lag structure, and temporal correlation.

The reanalyses largely confirmed the results obtained by the original investigators. Positive relationships were found between the PM index (TSP for Philadelphia, COH for Santa Clara, PM_{10} for the others) and mortality, and the resulting estimates were statistically significant except for Eastern Tennessee.

The sensitivity analyses for Philadelphia have added important new information to our understanding of the relationship between mortality and TSP when adequate data on copollutants are available, in this case for SO_2. As noted in the methodology discussion in Section 12.2, the analysis of copollutants in every other study has assumed an additive linear model in which each pollutant has an additional linear effect on excess mortality. While the validity of the linearity assumption has been examined in some studies using smooth nonparametric functions for the concentration-response model for a single pollutant, or using quartiles or quintiles of the air pollution variable as separators of categorical dummy variables, no other analysis of multiple pollutants has examined these two assumptions. Samet et al. (1995) used two-dimensional smoothing functions of TSP and SO_2 fitted to total mortality after adjustments for temperature, dew point, and time trends. Seasonality was controlled by indicator variables in the whole-year data set, and by fitting separate models for each season.

The results showed that, while segments of the TSP-SO_2 response surface were approximately linear, the concentration-response surface for both pollutants was clearly neither linear nor additive. There were intervals of the surface where there was little increase with respect to SO_2, but a large increase in excess mortality with increasing TSP; conversely there were ranges of TSP and SO_2 that showed a large increase in excess mortality with increasing SO_2 and little relationship to TSP, especially in winter. This demonstrates at least one case in which standard approaches to modeling response to multiple pollutants can be highly misleading. Attempts to interpret the effects of including one pollutant in the model on estimates of the regression coefficient or relative risk attributed to another pollutant have been based on an assumed linear relationship. While multicollinearity diagnostics can be informative in separating the effects of correlated pollutants in linear models, they may not be diagnosing the problem when the model is itself misspecified in terms of both the shape of the concentration-response and the interaction(s) among the multiple pollutants. This analysis sounds a cautionary note on the interpretation of published results about the sensitivity of RR estimates when

multiple pollutants are used in a model. The interrelationships of Philadelphia TSP and SO_2 by season are discussed further in Section 12.6.

The relationship between Philadelphia mortality and some potentially confounding pollutants has recently been reexamined by Samet et al. (1996a). They fitted models for total mortality, cardiovascular mortality, respiratory mortality, and mortality for other non-external causes, for the period 1974 to 1988. Models were fitted for whole-year data, using adjustments for weather, season, time trends, and for five pollutants: TSP, SO_2, O_3, NO_2, and CO. The results discussed in Section 12.6.2 are for whole-year total mortality with adjustments for averages of current-day and previous-day pollutant concentrations, and for a lagged CO variable denoted LCO that includes the two-day average CO from 3 and 4 days earlier as a predictor of total mortality in a Poisson regression model. They report results from their models somewhat differently than in this document, as the percent increase in mortality per increase in inter-quartile range (denoted IQR) of the pollutant. While we have established standard increments for TSP and SO_2, we have not defined standard increments for the effects of the other pollutants. In general, they find a statistically significant TSP effect when TSP, SO_2, O_3, NO_2, and LCO are all included in the model, with an excess mortality of about 1.06 percent for an IQR of 82.0 - 47.5 = 34.5 $\mu g/m^3$, or RR = 1.031 per 100 $\mu g/m^3$ TSP. The TSP effect is smaller (RR = 1.022) and only marginally significant when only SO_2 is included, slightly smaller (RR = 1.03) and statistically significant when only O_3 is included, and larger when other copollutants are included. See Section 12.6.2 for a more complete discussion.

Overall, qualitatively examining the recently conducted KM, BS, and TSP time-series studies summarized in Table 12-2 reveals that these various PM metrics are typically associated with mortality in most of the studies. The strength and interpretation of that association can vary depending on the number of other pollutants included and on the way they are considered in the analysis. In the above discussed cases where more pollutants were considered, other pollutants were often found to also be associated with mortality, sometimes less strongly and sometimes more strongly than for the PM metric. Moreover, in the cases where the correlations among the significant pollutants were reported, it was consistently found that the PM metric was correlated with these other pollutants. Thus, although these various analyses are strongly supportive of an ambient air pollution effect on mortality throughout the world and are generally consistent with the hypothesis of a PM effect on mortality, they are of limited usefulness in trying to

quantitatively assess PM mortality associations i.e., as a relative risk increases per μg/m^3 increase in thoracic particles (PM_{10}) or fine ($PM_{2.5}$) or coarse ($PM_{10-2.5}$) fractions of PM_{10}. Several studies that are more useful for devising such quantitative relationships are highlighted next.

PM_{10} Studies for the Utah Valley

Table 12-2 includes summaries of some recently reported PM_{10}-mortality studies, where PM_{10} was directly measured or calibrated for the site. Among these was a study of total, respiratory, and cardiovascular mortality in Utah County, UT during 1985 to 1989 (Pope et al., 1992). In this study, the various daily counts of mortality were regressed on the 5-day moving average PM_{10}, as well as on temperature, humidity, a time-trend term, and random year terms. While only one site was used to represent the whole county's PM_{10} level, comparisons with two other PM_{10} sites indicated spatial consistency (correlation between sites $\geq$ 0.95). Autoregressive Poisson methods were used because of the low total mortality counts (mean = 2.7/day) in this relatively small population (260,000). Using this model, a significant positive association was found between total non-accidental mortality and PM_{10}, and the authors concluded that a 100 μg/m^3 increase in the 5-day average PM_{10} concentration was associated with a 16% increase in mortality. Analyses presented indicate that the use of concurrent day PM_{10}, rather than a 5-day average, would have resulted in an effect estimate roughly half that reported in terms of the 5-day average PM_{10} (in deaths per μg/m^3). A "control" disease category (i.e., one unlikely to be affected by air pollution) was not considered per se. However, deaths due to causes other than respiratory or cardiovascular were considered, and found not to be associated with PM. Respiratory deaths were more strongly associated with PM_{10} than any other cause. These results support the biological plausibility of a PM-mortality association. Also, the PM_{10}-mortality association was found for PM levels well below the existing 24-h average PM_{10} standard of 150 μg/m^3. The authors dismiss other air pollutants as having negligible influence by comparing them to their respective present air quality standards without directly modeling the possibility that other (correlated) air pollutants might also influence mortality. On the other hand, Pope (1994) reported that PM_{10}, and SO_2 were only weakly correlated (r = 0.19), acid aerosol (H^+) levels were below 8 nmoles/m^3, and the introduction of O_3 into the model actually strengthened the PM_{10} association.

A reanalysis of deaths in Utah Valley, UT, from 1985 to 1992 was carried out by Lyon et al. (1995). The data were extensively categorized by year, season, cause, age, and place of death. Based on quintile plots, the authors concluded that excess mortality increased steeply at about 50 $\mu g/m^3$ and consequently used only a dichotomous indicator of PM_{10} greater than 50 $\mu g/m^3$, rather than any linear or nonlinear function of PM_{10}. No other pollutants were used, and the only meteorological variable used in the model was minimum daily temperature. Relative risk (called rate ratio) was calculated from a Poisson regression model without time series structure adjustment by GEE. However, a linear time trend was used to adjust for decreasing mortality rates over the years. The authors found an apparently random pattern of increased RR, by year, season, age, cause, and place of death. Among their results, they noted the following: strongest effect in spring, not winter; largest contribution to excess mortality from age 75 and over dying in hospital; largest RR for ages 15 to 59 dying at home from cancer; increased RR for sudden infant death syndrome. The choice of a 5-day mean PM_{10} as the exposure metric was based on an earlier study (Pope et al., 1992). However, dichotomizing the PM_{10} metric at 50 $\mu g/m^3$ may have cost a great deal of useful information, possibly including a substantial exposure measurement error or misclassification problem. Since this PM_{10} metric cannot be scaled to RR increments over other ranges of values, we were not able to include this study in the subsequent tables of this section. However, the authors estimate an excess mortality of 4% for PM_{10} above 50 $\mu g/m^3$, roughly consistent with other studies.

The Utah Valley mortality data have also recently been reanalyzed by Pope and Kalkstein (1996). This reanalysis evaluates a number of alternative approaches to controlling for weather-related variables and time trends, including nonparametric smoothing and the use of Kalkstein et al. (1987) Temporal Synoptic Index (TSI) climatological categories. The weather data from the Salt Lake City airport for 20 preceding years were used to create 19 categories of air mass types, each typically of several days' duration. The TSI and related methods are described in Section 12.6. The TSI method is essentially an objective procedure, based on clustering of principal components of 7 weather variables measured 4 times per day. The TSI categories are often closely identified with temperature and humidity differences that characterize different seasons, which allows a potentially more flexible approach than defining seasons by fixed calendar dates. Poisson regression analyses were performed on mortality data for April 7, 1985 (when PM_{10} monitoring began) through December 31, 1989. A large number of models were fitted to the

data, some of which are discussed in more detail in Section 12.6. Relative risk estimates for PM_{10} showed some sensitivity to model specification for time trends, but were consistently significant when long-term time trends were appropriately controlled, as by use of LOESS smoothers. Typical RR values were about 1.06 to 1.08 per 50 $\mu g/m_3$ PM_{10} for total mortality, consistent with earlier studies, and higher for death from cardiovascular causes (1.08 to 1.10) and for death from pulmonary causes (1.12 to 1.20).

The results showed very little sensitivity to variations in methods for controlling for weather-related effects, provided the methods had sufficient flexibility to model changes. Both the use of TSI categories and the adjustments using LOESS smoothers of temperature and dewpoint provided similar estimates of PM_{10} effects. While larger differences might be observed in communities with more variable climate conditions, this study suggests that the exact form of the weather model may not have a large effect on pollution estimates within a range of different methods. Additional comparisons in other communities are needed to evaluate the sensitivity of PM estimates to different methods of adjustment for weather.

PM_{10} Studies: St. Louis, MO and Kingston-Harriman, TN

Dockery et al. (1992) investigated the relationship between multiple air pollutants and total daily mortality during one year (September 1985 through August 1986) in two communities: St. Louis, MO; and Kingston/Harriman, TN and surrounding counties. In the latter locale, the major population center considered was Knoxville, TN, some 50 Km from the air pollution monitoring site employed. Total daily mortality in each study area was related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, H^+, temperature, dew point, and season using autoregressive Poisson models. In St. Louis, after controlling for weather and season, statistically significant associations were found with both prior day's PM_{10} and $PM_{2.5}$, but not with any lags of the other pollutants considered. In the Kingston/Harriman vicinity, PM_{10} and $PM_{2.5}$ approached significance in the mortality regression, while the other pollutants did not. In both cities, very similar PM_{10} coefficients are reported, implying a 8 to 9 percent increase in total mortality per 50 $\mu g/m^3$ of PM_{10}. While autocorrelation was accounted for, seasonality was only addressed by season indicator (dummy) variables, which could not address any within-season long wave influences. Also, in both places, only one daily monitoring station was employed to represent community exposure levels, and no information regarding the representativeness of these sites was provided

(e.g., correlations with other sites' data). Thus, using mortality data for Knoxville, TN (50 km from the Kingston/Harriman, TN monitoring site at which PM was measured) in the PM-mortality analysis raises questions about the representativeness of the exposure estimates used. Furthermore, the number of days for which pollution data are available for time-series analyses is limited in this data set, especially for H^+ (e.g., only 220 days had H^+ values at the St. Louis site). As stated by the authors: "Because of the short monitoring period for daily particulate air pollution, the power of this study to detect associations was limited." Nevertheless, despite these limitations, consistent PM_{10} coefficients were found for each of these two cities.

PM_{10} Studies: Birmingham

Total mortality-PM_{10} relationship in Birmingham, AL during August, 1985 through December, 1988 were evaluated by Schwartz (1993a). Poisson modeling was used to address small count effects (mean mortality = 17.1 deaths/day), season was addressed by the inclusion of 24 sine and cosine terms having periods ranging from 1 to 24 mo, and weather was modeled using various specifications of temperature and relative humidity. Autocorrelation was addressed using autoregressive parameters, as required, and day of week dummy variables were also included. In these analyses, significant associations were found between total daily mortality and the average of the three prior day's PM_{10} concentration. It was noted that averaging fewer days weakened the PM_{10}-mortality association, consistent with the expectation that multiple day pollution episodes are of the greatest health concern. The analysis did not look at any other pollutants, making it impossible to directly assess whether the association noted is due to PM_{10} alone or also in part to some other collinear pollutant (e.g., SO_2) not considered in the analysis. However, a variety of modeling approaches gave similar results, as did eliminating all days with PM_{10} >150 $\mu g/m^3$, indicating that the PM-mortality associations noted are not dependent on model choice or limited to elevated pollution days only.

PM_{10} Studies: Toronto

Özkaynak et al. (1994) related total daily mortality in Toronto, Ontario during 1972 to 1990 to daily PM_{10}, TSP, SO_4, CO, O_3, temperature, and relative humidity. A 19-day moving average equivalent high-pass filter was used to prefilter out long-wave cycles in the data and to

reduce autocorrelation. OLS regression was employed, as the distribution of mortality data tend toward the normal in larger cities such as Toronto (mean deaths = 40/day) once seasonal cycles are removed. In this dataset, 6,303 PM_{10} daily values were estimated based on TSP, SO_4, COH, visibility (i.e., Relative Humidity corrected B_{ext}, the extinction coefficient derived from airport visibility observations), and temperature data, using a model developed from 200 actual PM_{10} sampling days during the study period. This limits the usefulness of the results for distinguishing PM_{10} in the analyses, as it is derived from other PM metrics and from variables which may themselves be causally related to mortality (e.g., temperature). For example, estimated PM_{10} is correlated at r = 0.95 with TSP, and r = 0.27 with temperature. In the analyses, all pollutants considered were significantly associated with daily mortality. The simultaneous regression of total mortality on both O_3 and PM_{10} yielded significant coefficients for each. The PM_{10} mean effect (at 41 $\mu g/m^3$) was reported to be 2.3% of total mortality. However, the authors found that it was not possible to separate the PM_{10}-mortality association from that for other PM metrics considered.

PM_{10} Studies: Los Angeles

Kinney et al. (1995) investigated total daily mortality in Los Angeles, CA during 1985 to 1990 (mean = 153 deaths/day), relating it to PM_{10}, O_3, CO, temperature, and relative humidity to assess the sensitivity of the PM-mortality association to model type and model specification. Pollution data were averages of all sites available (e.g., 4 for PM_{10} and 8 for O_3 and CO), after first filling in missing days at each site based on available data from other sites (thereby addressing error from day to day variation in site availability). Although the data were collected over 6 years, the PM_{10} sampling was conducted only every sixth day; so, only 364 days could be included in the analysis, limiting its power to detect associations. Poisson models were used which addressed seasonal long wave influences by including sine and cosine terms ranging in periodicity from 1 to 24 mo in periodicity; OLS and log-linear models were also considered. Weather was modeled initially by including only same-day maximum temperature and relative humidity in regressions, but sensitivity analyses also considered dummy variables for extreme temperature and up to 3-d lags of all weather variables. Winter and summer were also modeled separately. In these various analyses, PM_{10} was generally found to be significantly associated with mortality after controlling for weather and season, with a relative risk (RR) estimate of

approximately 1.05 (CI = 1.0 to 1.10) reported for a 100 μg/m^3 increase in PM_{10}. Durbin - Watson (DW) statistics indicated only modest autocorrelation in these models (1.8<DW<2.0). The PM_{10}-mortality association was found to be only mildly sensitive to modeling method. However, CO was also significantly associated with mortality, and the simultaneous inclusion of either CO or O_3 to the PM_{10} model lowered the significance of PM_{10} in the model noticeably, but affected the coefficient less. The correlations among the pollutant's coefficients in this model were, however, significant ($r_\beta(PM_{10}\text{-}CO) = -0.4$; $r_\beta(PM_{10}\text{-}O_3) = -0.5$). Therefore, despite the effort made to maximize the quality of the exposure estimates and to appropriately address the statistical and multi-pollutant aspects of the analysis, the PM-mortality association was not completely separable from other copollutants. In this sense, these results are quite similar to those found previously for L.A. (Kinney and Ozkaynak, 1991).

PM_{10} Studies: Los Angeles and Chicago

Ito et al. (1995) considered total daily mortality during 1985 to 1990 in Los Angeles, CA (mean = 153 deaths/day) and Chicago, IL (mean = 117 deaths/day) in their investigation of the role of monitoring site choice on PM_{10} health effects analyses results. Poisson models were used which included four sine and cosine terms ranging from 1 to 24 mo in periodicity to control for season, day of week dummy variables, a linear trend term, and temperature. In each city, multi-site averages were computed for each pollutant considered (PM_{10} and O_3) after missing day's values were estimated at each site from other data available for that day. Also, simple daily averages of all available data were computed (without filling missing), and each site's raw data were also individually analyzed. The average of the multiple sites' PM_{10} was found to be significantly associated with total mortality in each city after controlling for season, temperature, and O_3. However, while the O_3 coefficient was only moderately correlated with the PM_{10} coefficient ($r_\beta = -0.2$), other potentially more correlated pollutants (e.g., CO, SO_2, or NO_2) were not considered in this basic model specification. Also, the size and significance of the PM_{10} coefficient in mortality regressions varied widely among the individual sites. The authors concluded that: "Thus, identification of a single causal pollutant, based simply on the strength of association with a health effect outcome without evaluation of attenuation/enhancement due to

random/systematic errors in exposure estimates, may be misleading." Dividing the data by season also diminished the significance of PM_{10} in mortality regressions, as would be expected due to reduced sample size. However, the PM_{10} coefficient was not as affected by season-specific analyses, indicating consistent associations throughout the year. Overall, multi-site averaging and larger sample sizes were shown to strengthen the PM_{10}-mortality association, but the results (and the fact that a very basic model specification was employed) leaves open the possibility that other co-pollutants or more elaborate weather specifications could account for part of the Chicago PM_{10} association with daily mortality.

PM_{10} Studies: Chicago/Cook County

Styer et al. (1995) considered total, respiratory, circulatory, and cancer deaths in Cook County, IL (Chicago). The mean number of total, respiratory circulatory, and cancer deaths in Cook County were 117 for all nonaccidental causes, 83 of them elderly (age 65 and over), 10 from respiratory causes (ICD 9 codes 11, 35, 472 to 519, 710.0, 710.2, 710.4), 56 from circulatory causes (ICD 9 codes 390 to 459), 28 from cancer (ICD 9 codes 140 to 209) per day. They also broke down total mortality by race and by sex. Exposure metrics were based on one daily station and up to 12 measurements per day from other monitoring stations in Cook County. Models were fitted using Poisson regression, with adjustments for mean daily temperature, specific humidity, and average daily pressure, but with no other air pollutant in the model. Pollen counts and other meteorological variables were evaluated but did not significantly improve one fitted model; semi-parametric and parametric models for PM_{10} were tested, with lags up to 5 days. Seasonal adjustments were significant.

The overall PM_{10} effect in Cook County was found to be statistically significant overall. However, Spring and Autumn showed significant PM_{10} effects, whereas Winter and Summer did not. Elderly mortality had twice the excess risk of total mortality. Respiratory deaths in Cook County had nearly three times the response to PM_{10} as total mortality, but was only marginally significant. The best PM_{10} predictor for most of the Cook County analyses performed by Styer et al. (1995) was a 3-day moving average (lags 0, 1, 2). While other PM_{10} lags were evaluated, no other pollutants were tested. The total mortality RR for 50 $\mu g/m^3$ PM_{10} in Cook County can be estimated as 1.04 (95% confidence interval 1.00 to 1.08) and is consistent with other studies. This study found a statistically significant cancer death effect that was about twice as high as the

PM_{10} effect on total mortality. The finding of a cancer death effect in a short-term study is unexpected and differs from the finding of no cancer effect in a TSP study in Philadelphia (Schwartz and Dockery, 1992a); thus, it may be a chance effect. However, cancer effects were identified in all three of the long-term prospective cohort studies discussed in Section 12.4.

PM_{10} Studies: Salt Lake County, Utah

Styer et al. (1995), in the same paper reporting on their Cook County findings, also described results obtained from analyses of PM_{10} relationships to elderly total daily mortality in Salt Lake County, UT. Date from two daily PM_{10} stations in Salt Lake County served as exposure metrics included in models fitted using Poisson regression, with adjustments for mean daily temperature, specific humidity, and average daily pressure. No other pollutants besides PM_{10} were considered in the models. Even without other pollutants in the models, Styer et al. (1995) reported finding no effect of PM_{10} on elderly mortality in Salt Lake County, UT.

PM_{10} Studies: Santiago, Chile

Ostro et al. (1996) considered total, respiratory, and cardiovascular daily deaths (mean = 55, 8, and 18 deaths/day, respectively) in Santiago, Chile during 1989 to 1991, examining their relationship to ambient PM_{10}, O_3, SO_2, and NO_2, and to daily minimum and maximum temperature and humidity. To improve exposure estimate representativeness, multiple sites' daily data were averaged for each pollutant (e.g., 4 sites for PM_{10}), though the maximum from all 4 PM_{10} sites for each day was also considered in some analyses. In this work, most regressions employed the log of PM_{10}, as it showed the highest associations with total mortality in exploratory analyses.

OLS regression was employed for most total mortality regressions because a test of normality was not rejected for the total mortality data, though Poisson regressions were used for cause-specific analyses in view of their lower daily counts. Also, sensitivity analyses were conducted for various model types: the total mortality RR of the mean PM_{10} concentration (115 $\mu g/m^3$) ranged from 1.04 to 1.09 (1.12 with a 3-day average mean PM_{10} employed). Seasonal influences were also addressed by various methods, including seasonal stratification, the inclusion of sine/cosine trigonometric terms for 2.4, 3, 4, 6, and 12 mo periodicities, prefiltering, and the use of various non-parametric fits of temperature: the PM_{10} RR estimate ranged from

1.04 to 1.11, with the lowest mean PM_{10} risk provided by the OLS model with 5 trigonometric terms included (RR = 1.04). Investigations of mortality by-cause and age found the strongest PM_{10} associations for respiratory-specific deaths (RR = 1.15) and for the elderly (RR = 1.11). Other pollutants were also considered separately and simultaneously with PM_{10} in a total mortality regression which also contained 36 dummy variables (one for each month of the study). In this model, the individually significant pollutants were: log(PM_{10}) (RR at mean = 1.05 ; CI = 1.01 to 1.08); SO_2 (RR at mean = 1.01; CI = 1.00 to 1.03), and; NO_2 (RR at mean = 1.02 ; CI = 1.01 to 1.04). Thus, all three pollutants had similar levels of significance in this model, but only log(PM_{10}) stayed significant in multi-pollutant regressions. The intercorrelations of the various pollutants' coefficients were not reported, but they were likely high, given that the pollutants themselves were highly intercorrelated over time, e.g., r(PM_{10}-NO_2) = 0.73. Overall, these results suggest that, of the pollutants considered, PM_{10} is the air pollutant most strongly associated with mortality in this setting; and the sensitivity analyses suggest that the elderly with respiratory diseases were most susceptible to ambient air pollution effects.

Time Series Analyses Comparing PM_{15}, Fine, and Coarse Thoracic Particles

The daily time series data from the Six City Study has recently been reanalyzed (Schwartz et al., 1996) using statistical methods for Poisson data similar to those used in most other recent studies. This study extended the Dockery and Schwartz (1992) analyses to four additional regions, and also included separate analyses for fine particles ($PM_{2.5}$, denoted FP) coarse fractions particles (PM_{15} - $PM_{2.5}$ denoted CP), sulfates and acidity. The PM_{15} and $PM_{2.5}$ studies were carried out between 1979 and 1987, with daily samples ranging from 1,140 in Boston up to 1,520 in Steubenville. Poisson time series regression models were fitted, with statistical adjustments for time trends, temperature, and dew point using nonparametric smoothers in a generalized additive model. Since 62% of the $PM_{2.5}$ daily samples did not have a previous-day $PM_{2.5}$ measurement, lag structures were not examined. However, the exposure metric for each day was assumed to be the mean of the available non-missing current or previous day $PM_{2.5}$ values, which increased the total data set used from 7,436 to 12,055 observations. The acid aerosol measurements were, however, only available for 159 to 429 days in each of six regions. No $PM_{2.5}$ or PM_{10} analyses were presented based only on the reduced subset of days for which

H^+ data were available, which would have allowed more specific comparisons of the goodness of fit of H^+ with other PM indices.

The results for PM_{15} showed that very similar increases in daily mortality associated with thoracic particles occurred in five of the six cities, with RR ranging from 1.030 to 1.061 per 50 $\mu g/m^3$ PM_{15} except in Topeka, which had negative excess PM_{15} risk. The results were statistically significant except in Portage and Topeka.

Furthermore, of much interest, there were very similar increases in daily mortality associated with fine particles in all six cities, with RR ranging from 1.020 to 1.056 per 25 $\mu g/m^3$ $PM_{2.5}$. The results were statistically highly significant in Harriman-Kingston, St. Louis, and Boston, and nearly so in Portage and Steubenville. The effect size was similar in magnitude, but not significant in Topeka.

In contrast, coarse fraction particles (PM_{15} - $PM_{2.5}$) showed small and non-significant RR values, except for Steubenville (RR = 1.061 per 25 $\mu g/m^3$ CP). Excess risk was again negative for Topeka, and RR ranged from only 1.005 to 1.025 per 25 $\mu g/m^3$ for the four other cities. Based on these results, the authors concluded that, in most cases, associations between excess mortality and inhalable particles appears to be derived mainly from the fine particle fraction. Even in the case of Steubenville, the significant coarse particle-mortality associations may be due to fine partilce effects, given that the coarse particle levels were highly correlated with $PM_{2.5}$ concentrations.

When data for all six cities were combined, the combined estimate of the effects of PM_{15} and $PM_{2.5}$ were even more highly significant, with $PM_{2.5}$ definitely more predictive than PM_{15}. The combined estimate for CP was marginally significant, probably reflecting the significant contribution of Steubenville. Similar estimates were carried out for sulfates and for acid aerosols. The sulfate component was a statistically significant predictor of excess mortality, although less so than either PM_{15} or $PM_{2.5}$. H+ was not significant, even with 1,621 days of data in four cities, but the power of the H^+ analyses was lower than for the other PM indices. Thus, although the anomalous Steubenville CP findings cannot be entirely ignored, the overall pattern of results most clearly implicates fine particle indicators as being most strongly and consistently associated with increased daily mortality in the Six-City Study database.

The authors also evaluated a possible nonlinear relationship by considering only days with $PM_{2.5}$ less than 25 or less than 30 $\mu g/m^3$. The fitted log-linear relationship was larger in

magnitude than when all $PM_{2.5}$ days were included, RR = 1.056 (CI 1.035 to 1.077) per 25 $\mu g/m^3$ on days with $PM_{2.5} < 25$ $\mu g/m^3$.

Additional analyses explored specific causes of death. The excess risk of death by ischemic heart disease associated with $PM_{2.5}$ was about 40% higher than for all-cause nonexternal mortality, and more than twice as high for death by pneumonia and by COPD.

12.3.1.2 Short-Term PM_{10} Exposure Associations with Total Daily Mortality: Syntheses of Studies

Most of the studies summarized in Table 12-2 and discussed in more detail above considered daily mortality in the entire population (i.e., all ages) and due to all causes, although some also considered sub-populations. Considering all of these studies in one overall assessment of PM effects on mortality is not a straightforward task, given the variety of models and model specifications employed but, as noted above, this has been attempted previously. Table 12-3 presents intercomparisons of PM-daily mortality results based on of two recently published summaries of the PM literature which attempted to convert all results to a PM_{10}-equivalence basis and to provide quantitative intercomparisons (Ostro, 1993; Dockery and Pope, 1994b). As also noted above, other such syntheses have been conducted using TSP as the reference PM metric (Schwartz, 1992a, 1994b), but many of the same studies were considered in thetwo PM_{10}-equivalent summaries, so the TSP-equivalent results are not tabulated here.

The results presented in Table 12-3 suggest about a 1 percent change in acute total mortality for a 10 $\mu g/m^3$ change in PM_{10}, but the estimates range from 0.3 to 1.6% (i.e., a factor of 5). It is important to note that other air pollutants have generally not yet been addressed in reaching these reported PM coefficients. While most of the 95% confidence intervals (CI's) of the PM estimates overlap, CI's of the highest and lowest estimates do not overlap, indicating significant differences between these estimates. The effects indicated for a 10 $\mu g/m^3$ change cannot be consistently converted to other PM increments (e.g., 50 or 100 $\mu g/m^3$ PM_{10}), as differences in model specification (e.g., linear versus log models) will cause them to differ in their conversions to other particle concentration levels. Reasons for the approximately five-fold effect estimate difference noted among studies are not obvious from the information provided by these references, but one factor appears to be the PM exposure averaging time, as estimates using multiple day PM_{10} averages are all 1% or higher. This is not unexpected, given that (in the absence of a strong harvesting effect) any lagged effects from prior days of PM_{10} exposure would be added to the effects estimate when a multi-day average is employed, increasing the estimated effect on a per $\mu g/m^3$ basis. Also, PM coefficient variation can be expected, given that the composition (and, therefore, toxicity) of the PM, as well as the population make-up, in each city can be expected to differ. Moreover, the conversions from other PM metrics to PM_{10} must necessarily introduce additional uncertainty. This is made apparent here when comparing the estimates for Santa Clara, CA from the two listed references, each having its own somewhat

different estimate of the equivalent PM_{10} and of the PM_{10} effect. Although not all of these results may therefore be the most appropriate available for quantifying a PM_{10} effect, they do indicate a consistent association between acute PM exposure and increased daily mortality. Moreover, the by-cause results also reported in these summaries indicate that PM effect estimates are greater for respiratory causes, lending support to the biological plausibility of the PM associations.

In an attempt to better quantify daily PM_{10}-total acute mortality associations indicated by the above discussions, Table 12-4 presents a summary of the total mortality relative risks (RR) of a 50 $\mu g/m^3$ increase in PM_{10} estimated from nine studies reviewed above which employed PM_{10} data in their analysis of total mortality data (or which had on-site PM_{10} reference data to convert other PM metrics with more certainty). This selection of studies does not mean to dismiss the other studies discussed above as less important; the studies selected, however, can most readily be intercompared and referred to the present PM_{10} standard. The RR's calculated were based upon a 50 $\mu g/m^3$ increase above the mean PM_{10}, which is the order of magnitude of the difference between the maximum and mean in these cities and roughly approximates the estimated effects of a typical day experiencing an exceedance of the present PM_{10} standard, relative to the average case. This is important to note, because in non-linear models such as were often employed in the studies in Table 12-3, the RR estimate associated with a given $\mu g/m^3$ PM_{10} increase will vary depending upon the baseline concentration to which it is added.

From the results presented in Table 12-4, it is apparent that these studies generally have yielded at least marginally significant PM_{10} coefficients, but that the resultant excess risk estimates vary by a factor of five across these studies (from 1.5% to 8.5% per 50 $\mu g/m^3$ for the year-round analyses). The mean and maximum PM_{10} concentration data are noted for each study. If the PM_{10} coefficient increased as the mean level of PM_{10} decreased, then confounding or non-linearity might be suspected. However, the data presented indicate that the variability in coefficients is not a function of PM_{10} level, as sites with high or low PM_{10} concentrations can report either high or low RR's. In Table 12-5, an attempt is made to concisely summarize the statistical methodology characteristics of each study, in order to

TABLE 12-4. COMPARISON OF RELATIVE RISK (RR) ESTIMATES FOR TOTAL MORTALITY FROM A 50 $\mu g/m^3$ INCREASE IN PM_{10}, USING STUDIES WHERE PM_{10} WAS MEASURED IN THE UNITED STATES OR CANADA[a]

Study	Reference	PM_{10} ($\mu g/m^3$)		Other Pollutants In Model	Lag Times, d	RR per 50 $\mu g/m^3$	95 Percent Confidence Interval
		Mean	Maximum				
Utah Valley, UT	Pope et al. (1992)	47	297	None	≤ 4 d	1.08	(1.05, 1.11)
	Pope and Kalkstein (1996)	47	365	None	≤ 4 d	1.07	(1.02, 1.12)
Birmingham, AL	Schwartz (1993a)	48	163	None	≤ 3 d	1.05	(1.01, 1.10)
St. Louis, MO	Dockery et al. (1992)	28	97	None	≤ 3 d	1.08	(1.005, 1.15)
	Schwartz et al. (1996)	31		O_3	≤ 3 d	1.06	(0.98, 1.15)
				None	≤ 1 d	1.03	(1.005, 1.05)
Kingston, TN	Dockery et al. (1992)	30	67	None	≤ 3 d	1.085	(0.94, 1.25)
	Schwartz et al. (1996a)	32		O_3	≤ 3 d	1.09	(0.94, 1.26)
				None	≤ 1 d	1.05	(1.005, 1.09)
Portage, WI	Schwartz et al. (1996a)	18		None	≤ 1 d	1.035	(0.98, 1.09)
Boston, MA	Schwartz et al. (1996a)	24		None	≤ 1 d	1.06	(1.04, 1.09)
Topeka, KS	Schwartz et al. (1996a)	46		None	≤ 1 d	0.98	(0.90, 1.05)
Steubenville, OH	Schwartz et al. (1996a)	46		None	≤ 1 d	1.05	(1.005, 1.08)
Toronto, ON Canada	Özkaynak et al. (1994)	40	96	None	0 d	1.025	(1.015, 1.034)
Los Angeles, CA	Kinney et al. (1995)	58	177	None	1 d	1.025	(1.00, 1.055)
				O_3, CO	1 d	1.017	(0.99, 1.036)
Chicago, IL	Ito et al. (1995)	38	128	O_3, CO	≤ 3 d	1.025	(1.005, 1.05)
Chicago, IL	Styer et al. (1995)	37	365	None	3 d	1.04	(1.00, 1.08)
Chicago, IL	Ito and Thurston (1996)	41	>65[b]	None	≤ 1 d	1.025	(1.005, 1.04)
				O_3	≤ 1 d	1.02	(1.005, 1.035)

[a]Calculated on basis of 50 $\mu g/m^3$ increase, from 50 to 100 $\mu g/m^3$ PM_{10}.
[b]90th percentile.

TABLE 12-5. ADDITIONAL INFORMATION ON TIME SERIES STUDIES OF PM_{10}-MORTALITY CITED IN TABLE 12-4

Study	Reference	Period	Other Pollutants In Model	Lags Addressed		Multiple Methods	Correl. of B's Given	No. of Obs.
				Pollutants	Temp			
Utah Valley, UT	Pope et al. (1992)	1985-1989	None	0-4 d	≤ 1 d	Yes	No	1,436
St. Louis, MO	Dockery et al. (1992)	1985-1986	$PM_{2.5}$, SO_4, H^+, SO_2, NO_2, O_3	≤ 3 d	≤ 1 d	No	No	311
Kingston, TN	Dockery et al. (1992)	1985-1986	$PM_{2.5}$, SO_4, H^+, SO_2, $NO_{2.5}$, O_3	≤ 3 d	≤ 1 d	No	No	330
Birmingham, AL	Schwartz (1993a)	1985-1988	None	0-3 d	≤ 3 d	Yes	No	1,087
Toronto, ON Canada	Özkaynak et al. (1994)	1972-1990	TSP, $PM_{2.5}$, SO_4, O_3, COH, NO_2, SO_2	0 d	0 d	No	No	6,506
Los Angeles, CA	Kinney et al. (1995)	1985-1990	O_3, CO	1 d	≤ 3 d	Yes	Yes	364
Chicago, IL	Ito et al. (1995)	1985-1990	O_3, CO	≤ 3 d	≤ 3 d	No	Yes	1,357
Chicago, IL	Styer et al. (1995)	1985-1990	None	≤ 5 d	≤ 2 d	Yes	No	1,357

determine if any of these factors are important to the variability observed from study to study in the PM_{10} RR estimate. Of all factors examined in this table, the one most consistently present with higher PM_{10} RR's is when other pollutants have not been simultaneously considered in the model. Indeed, those studies which considered PM_{10} both alone and with other pollutants in the model yielded consistently smaller (and usually more marginally significant) PM_{10} relative risks when the other pollutants were simultaneously considered. This influence ranges from roughly a 20 to 50 percent reduction in the excess risk associated with 100 $\mu g/m^3$ in PM_{10} (e.g., in Athens, Greece, the PM_{10} RR declines from 1.07 to 1.03 when other pollutants are considered). However, such a reduction is to be expected when colinear variables are added, and the "true" PM_{10} RR is likely to lie between the single pollutant and multi-pollutant model estimates, provided that the pollutant variables and other covariates are relatively free of measurement error and that the regression model is correctly specified.

Another factor which clearly affected the PM_{10} RR from some of the studies listed in Table 12-4 was the PM_{10} averaging period. Both of the studies which utilized multi-day averages of PM_{10} in their regressions (i.e., Utah Valley, UT and Birmingham, AL) are among the higher RR estimate studies. As discussed above, this would be expected, but the increase indicated for these studies is not as large as might be expected. Indeed, in sub-analyses included by Pope et al. (1992), the PM_{10} mortality risk is indicated to be roughly doubled by using a five day average versus a single day concentration, while sub-analyses presented by Ostro et al. (1996) for Santiago also indicate approximately a doubling in the PM_{10} RR when a 3 day average is considered (i.e., from RR = 1.04 for a single day PM_{10} value to RR = 1.07 for a 3d average PM_{10} value). This may be due to the fact that, since correlation exists over time in the PM_{10} concentrations, the single day concentration is "picking up" some of the effect of multi-day pollution episodes, even though they are not explicitly modeled. Also, most studies show a maximum same-day or one day lag PM-mortality association, with the PM_{10} regression coefficient decreasing on subsequent days.

It appears from Table 12-4 that the total acute mortality relative risk estimate associated with a 50 $\mu g/m^3$ increase in the one-day 24-h average PM_{10} can range from 1.015 to 1.085 in year-round analyses, depending upon the site (i.e., the PM_{10} and population composition) and also upon whether PM_{10} is modeled as the sole index of air pollution. Relative Risk estimates with PM_{10} as the only pollutant index in the model range from RR = 1.025 to 1.085, while the

PM_{10} RR with multiple pollutants in the model range from 1.015 to 1.025. The former range might be viewed as approximating an upper bound of the best estimate, as any mortality effects of co-varying pollutants are likely to be "picked up" by the PM_{10} index, while the multiple pollutant model range might be viewed as approximating a lower bound of the best estimate, assuming that other co-pollutants are controlled for, as the inclusion of highly correlated covariates are likely to weaken the PM_{10} estimate, even if they are not themselves causal. Both estimates should be considered in assessing the potential effects of PM_{10}. Overall, consistently positive PM-mortality associations are seen throughout these analyses, despite the use of a variety of modeling approaches, and even after steps were taken to statistically control major confounders such as season, weather, and co-pollutants, with the 24-h average 50 $\mu g/m^3$ PM_{10} total mortality effect estimate apparently being in approximately the RR = 1.025 to 1.05 range. Comparison of alternative PM exposure indices as well as other pollutants, can also be done using elasticity as a dimensionless index of relative risk (Lipfert and Wyzga, 1995b).

12.3.1.3 Short-Term PM_{10} Exposure Associations with Daily Mortality in Elderly Adults

Of the studies in Tables 12-2 to 12-5 discussed above, only a few directly examined the elderly as a potentially sensitive sub-population. Certainly, since the highest mortality rates are among the elderly, this is a population which surely dominated the total mortality analyses discussed above, and it is therefore logical to assume that the bulk of the total mortality effects suggested by these studies are among the elderly. Also, as noted earlier, during the historic London, 1952 pollution episode the greatest increase in mortality rate was among older citizens and those with respiratory diseases. More recently, an analysis by Schwartz (1994c) of mortality in Philadelphia, PA during 1973 through 1980 comparing mortality during the 5% highest versus the 5% lowest TSP days found the greatest increase in risk of death among those aged 65 to 74 and those >74 year of age (mortality risk ratios = 1.09 and 1.12, respectively, between high and low TSP days). Also, in their time series analyses of Philadelphia daily mortality during this period, Schwartz and Dockery (1992a) found a significantly higher TSP-mortality coefficient (ß = 0.000910 ± 0.000161) for persons older than 65 years of age than for the younger population (ß = 0.000271 ± 0.000206). These coefficients indicated an effect size for the elderly roughly three times that for the younger population (10% versus 3%, respectively, for a 100 $\mu g/m^3$ TSP increase).

In addition, two recent PM_{10} analyses which directly considered the question of PM_{10}-mortality associations among the elderly population (≥ 65 years of age), provide further relevant insights into this question. The first of these two analyses was conducted by Saldiva et al. (1994) during May 1990 through April 1991 in Sao Paulo. Environmental variables considered included PM_{10}, SO_2, NO_x, O_3, CO, temperature, and humidity. PM_{10} was not measured gravimetrically, but rather by beta gauge instrument readings calibrated to mass. Pollutants were considered in the analysis in the form of 2-day moving averages (i.e., averages of the same-day and the prior day's concentration). Monitoring data from multiple sites were averaged for each pollutant (e.g., 8 sites for PM_{10}). Multiple regression models estimated the association between daily mortality and air pollution controlling for month of year, temperature, relative humidity, and day of week. Because of the large number of daily deaths (mean = 63/day), Gaussian regression models were appropriately used for the basic analysis. Poisson models using the generalized estimating equation of Liang and Zeger (1986) were also applied for comparison. Temperature effects were crudely accounted for through the use of three dummy variables ($T < 8\ ^\circ C$; $8\ ^\circ C \leq T \leq 12\ ^\circ C$; $13\ ^\circ C \leq T \leq 18\ ^\circ C$) in the basic model. Regression results indicated that, when studied separately, PM_{10}, SO_2, NO_x, and CO were all significantly associated with mortality. In a simultaneous regression of mortality on all pollutants, however, PM_{10} was the only pollutant that remained significant. In fact, the PM_{10} coefficient actually increased, suggesting confounding among these correlated pollutants. Thus, as noted by the authors, "the close interdependence exhibited by the concentrations of measured pollutants suggests that one has to be cautious when ascribing to a single pollutant the responsibility of causing an adverse health effect". Nevertheless, multiple regression models, including those considering all pollutants simultaneously, consistently attributed the association found with mortality among the elderly to PM_{10}. The reported PM_{10} relative risk (RR = 1.13 for a 100 $\mu g/m^3$ increase) is higher than noted above for total mortality studies addressing multiple pollutants (100 $\mu g/m^3$ RR ≈ 1.03 to 1.05), supporting past observations that the elderly represent a population especially sensitive to health effects of air pollution.

A second recent study directly examining PM_{10}-mortality associations in the elderly was that by Ostro et al. (1996) in Santiago, Chile. For the overall population, the 100 $\mu g/m^3$ PM_{10} RR estimate was 1.08, but for the population aged 65 and greater, it rose to an estimate of RR = 1.11 in the same model specification. Thus, these directly comparable estimates (i.e., using the

same model specification and population) suggest that the elderly experience roughly a 40 percent higher excess risk from exposure to PM air pollution than the total population.

In contrast to the consistent results across the several studies described above, it should be noted that the analysis of deaths in the elderly population in France by Derriennic et al. (1989) discussed previously found no associations with TSP, whereas SO_2 was associated with total elderly deaths in both cities studied. No PM_{10} or fine particle metric was considered, however. Also, Li and Roth (1995) reported no significant association between TSP and daily deaths in the elderly in Philadelphia.

Overall, considering the historical pollution episode evidence and the results of recent PM_{10}-mortality analyses considering elderly populations, elderly adults appear to represent a population especially at risk to the mortality implications of acute exposure to air pollution, including PM.

12.3.1.4 Short-Term PM_{10} Exposure Associations with Daily Mortality in Children

As with analyses of PM-mortality associations for the elderly, few studies have directly examined PM-mortality associations in children. While the previously discussed London Fog episode yielded the greatest increased risk in the older population (e.g., the episode mortality risk versus the week before the episode increased by a factor of 2.74 for persons >45 years old), the second highest increase in risk was in the neo-natal group (ratio = 1.93 for children < 1 year) (United Kingdom Ministry of Health, 1954). More recently, as described above, Schwartz (1994c) examined increased risk of death in Philadelphia, PA for relatively high versus low TSP days during 1973 to 1980 by age, but concluded that no pattern of increased risk emerged until age 35 and above (e.g., the high/low TSP mortality ratio for < 1 year of age was 1.01). The author noted increased risk of death on high PM days for children 5 to 14 years old, which he suggested may be due to their greater time spent outdoors than other ages, though he notes that the small numbers of deaths in this age group suggest caution in such interpretations.

A recent analysis of PM_{10} pollution and mortality in Sao Paulo, Brazil provides further insight into the potential mortality effects of PM_{10} on children. Saldiva et al. (1994) studied respiratory mortality among children < 5 yrs old in Sao Paulo during May 1990 to April 1991. The environmental variables considered included PM_{10}, SO_2, NO_x, O_3, CO, temperature, and humidity. PM_{10} was not measured gravimetrically, but by beta gauge readings calibrated to

mass. Pollutants were considered in the analysis in the form of 3-day moving averages of concentration (i.e., averages of the same-day and the two prior day's concentrations). Monitoring data from multiple sites were averaged for each pollutant (e.g., 8 sites for PM_{10}). Prior to the analysis, mortality counts were adjusted using a square root transformation to address their non-normal distribution, which results in part from low daily counts (mean = 3.0 deaths/day). Season was addressed by including both seasonal and monthly dummy variables in all regressions. Weather was only crudely addressed, in that only two dummy variables for extreme temperature and two for extreme relative humidity were considered. Day-of-week effects were addressed by the inclusion of six dummy variables, but none were significant. Autocorrelation was not directly addressed in the analyses. Despite the limited data set size, a significant mortality association was found with NO_x, but not with any other pollutant. No such association was found for non-respiratory mortality, which is supportive of the interpretation of the air pollution-respiratory mortality association as causal. In the multiple pollutant model, the PM_{10} coefficient actually becomes negative (though non-significant), which is likely due to its high intercorrelation with NO_x over time ($r = 0.68$). The high interdependence between NO_x and most of the other pollutants caused the authors to note that "interplay among pollutants causing respiratory damage is very difficult to exclude". Thus, while there appeared to be an air pollution association with mortality in children, this study found the strongest association with NO_x, though the high intercorrelation among pollutants makes it difficult to designate the effects noted to any one pollutant in this case.

Overall, there is an indication among these various analyses that children could be susceptible to the mortality effects of air pollution exposure in general but it is difficult, given the limited and somewhat conflicting available results, to ascribe any such association to PM pollution in particular.

12.3.1.5 Short-Term PM_{10} Exposure Associations with Daily Mortality in Other Susceptible Subgroups

Throughout the results and discussions presented above regarding the effects of acute PM exposure on human mortality, a consistent trend was for the effect estimates to be higher for the respiratory mortality category. This lends support to the biological plausibility of a PM air pollution effect, as the breathing of toxic particles would be expected to most directly affect the respiratory tract and these results are consistent with this expectation. For example, the

respiratory mortality relative risk estimates presented in Table 12-3 are all higher than the risks for the population as a whole. Of particular interest is to compare the relative risk values for each study, which yield the most direct and appropriate comparisons as follows for: (a) the Santa Clara study (Fairley, 1990), where the respiratory mortality RR of PM was 4.3 times as large as for deaths as a whole (i.e., 3.5/0.8, in Table 12-3); (b) the Philadelphia, PA study (Schwartz and Dockery, 1992a), where the respiratory mortality RR of PM was 2.7 times as large as for death as a whole (i.e., 3.3/1.2, in Table 12-3); (c) the Utah Valley study (Pope et al., 1992), where the respiratory mortality RR of PM_{10} was 2.5 times as large as for deaths as a whole (i.e., 3.7/1.5, in Table 12-3); and (d) the Birmingham, AL study (Schwartz, 1993a), where the respiratory mortality RR of PM_{10} was 1.5 times as large as for deaths as a whole (i.e., 1.5/1.0, in Table 12-3). More recently, the Santiago, Chile PM_{10} study by Ostro et al. (1996), reported that the respiratory mortality RR of PM_{10} was 1.8 times as large as for deaths as a whole (i.e., 1.15/1.08 RR for a 100 $\mu g/m^3$). Thus, in these studies, the PM RR for respiratory diseases is indicated to range from 50% to over 400% higher for respiratory disease categories than for all causes of death, indicating that increases in respiratory deaths are a major contributor to the overall PM-mortality associations noted previously. Moreover, since evidence suggests that an acute pollution episode is most likely inducing its primary effects by stressing already compromised individuals (rather than, for example, inducing chronic respiratory disease from a single air pollution exposure episode), the above results indicate that persons with pre-existing respiratory disease represent a population especially at risk for mortality implications of acute exposures to PM-related air pollution.

12.3.1.6 Conclusions

In overall summary, the time-series mortality studies reviewed in this and past PM criteria documents provide strong evidence that ambient air pollution is associated with increases in daily human mortality. Recent studies provide confirmation that such effects occur at routine ambient levels and suggest that such effects extend below the present U.S. air quality standards. Furthermore, these new PM studies are consistent with the hypothesis that PM is a causal agent in the mortality impacts of air pollution. Overall, the PM_{10} relative risk estimates derived from the most recent PM_{10} total mortality studies suggest that an increase of 50 $\mu g/m^3$ in the 24-h average of PM_{10} is associated with an effect of the order of RR = 1.025 to 1.05 in the general

population, with even higher relative risks indicated for the elderly sub-population and for those with pre-existing respiratory conditions, both of which represent sub-populations especially at risk to the mortality implications of acute exposures to air pollution, including PM.

There is relatively little information on acute mortality effects associated with fine particles ($PM_{2.5}$) and coarse particle (PM_{10} - $PM_{2.5}$) components of PM. The recent analyses by Schwartz et al. (1996) greatly extend the previous investigations of data from the Six City Study. The relationship between excess mortality and $PM_{2.5}$ is similar in magnitude in all six cities (RR from 1.026 to 1.055 per 25 $\mu g/m^3$ $PM_{2.5}$) and statistically significant in five of the six cities. The relationship between excess mortality and coarse particles is much smaller and not significant in four of these cities, negative for Topeka (where the coarse particles are predominantly of crustal origin) and statistically significant only for Steubenville (where the coarse particles are probably predominantly from industrial combustion sources), RR = 1.053 per 25 $\mu g/m^3$. The relationship between excess mortality and sulfates is somewhat weaker than for $PM_{2.5}$, but still statistically significant. The relationship with aerosol acidity is even smaller, and not statistically significant. It is also not clear whether the large and statistically significant effects of fine particles on mortality should be attributed to the sulfate fraction of $PM_{2.5}$, or whether there is similar risk associated with the non-sulfate components. It is not clear whether to attribute the predictiveness of sulfates to the fact that sulfates are fine particles, or to some other property such as their acidity, even though aerosol acidity may not have been as adequately characterized in the Six City Study. This is because the data base is so much smaller than for sulfates and particles as H^+ was monitored on only 18% as many days as PM_{10} and $PM_{2.5}$. Even when monitored, H^+ was below the detection limit on many days, which further limited the data set. Finally, these analyses show that while coarse particles appear to play a much smaller role in acute mortality than fine particles, there may be at least some situations (such as in Steubenville) where coarse fraction particles cannot be entirely ruled out as possibly contributing to excess mortality along with fine particles.

12.3.2 Morbidity Effects of Short-Term Particulate Matter Exposure

12.3.2.1 Hospitalization and Emergency Visit Studies

Introduction to Hospitalization Studies

Hospitalization for a respiratory illness diagnosis can provide a measure of the respiratory morbidity status of a community during a specified time frame. Such respiratory diagnoses include hospitalization for pneumonia, influenza, and asthma. Various factors affect the epidemiology of admissions for these diagnosis. Factors shown to be independently associated with respiratory hospitalization include poor socioeconomic level, type of heating, and exposure to second-hand tobacco smoke (Thomson and Philion, 1991).

Beard et al. (1992) evaluated interobserver variability during data collection for a population based study of asthma using medical record information. The results suggested that data collection was carried out reliably in this study. Osborne et al. (1992) evaluated the diagnosis of asthma in 320 inpatient and outpatient records bearing the diagnosis of asthma for the period 1970 through 1973 and 1980 through 1983 in a health maintenance organization (HMO). The majority of charts examined exhibited a clinical picture consistent with asthma. The increases in "definite asthma" among outpatients from the 1970s to the 1980s reflected increasing chart documentation among physicians. Jollis et al. (1993) study of hospital insurance claim information to include medicare indicated that insurance claim data lack important diagnostic and pragmatic information when compared with concurrently collected clinical data in the study of ischemic heart disease as an example.

Wennberg et al. (1984) found that hospital admissions for the following diagnosis- related groups showed a very high variation by hospital market area: pediatric pneumonia, pediatric bronchitis and asthma, chronic obstructive lung disease, and adult bronchitis and asthma. Richardson et al. (1991) found that adjusted admission rates for respiratory distress (COPD, asthma, bronchitis, and pneumonia) varied up to 3.09-fold between the highest and lowest hospital market areas in 1986 for the state of Ohio. The reasons for differences between hospital market areas are found in the incidence of illness, variability of local resources, access to care, practice styles of area physicians, numbers of physicians and pulmonologists, inconsistencies in diagnoses, conflicting treatment methodologies, lack of consensus of care, quality of outpatient care, and varying criteria for admission among principal variables. For example, Wennberg et al. (1984) documented great geographic variability in hospital admission rates for adult community acquired pneumonia. This variation suggests that physicians do not use consistent criteria for hospitalization. Specific indications for admission do exist such as the Appropriateness Evaluation Protocol (AEP). Substitution of outpatient for inpatient care is a

major strategy promoted to reduce health care cost and as such the majority of patients with community acquired pneumonia are treated as outpatients.

Fedson et al. (1992) state that vaccination practices may play a role in hospitalization rates for influenza and associated respiratory disorders. Despite public health recommendations for influenza vaccination for elderly persons, the vaccine has not been widely used, in the United States only 32% of elderly persons may be vaccinated each year. During the influenza outbreak period most persons with respiratory conditions requiring hospitalization (92%) resided in private residence rather than in nursing homes. Also while previous epidemiologic studies arbitrarily defined outbreak periods as the first three months of the year this study indicated that hospitalization discharges for influenza mainly occurred during the period December 1 through February 28.

The number and rate of patients discharged by age and first-listed diagnosis in the United States in 1991 are shown in Table 12-6 for all conditions, respiratory disease, heart and circulatory diseases and neoplasma. Disease of the respiratory system represent approximately 10% of all conditions. The number and rate for pneumonia of the respiratory diseases listed in Table 12-6 are highest for all ages primarily due to the high number and rate for 65 years and over. Specific diseases of the respiratory system are shown in Table 12-7 for 1992, in which five groupings predominate. "Pneumonia organism unspecified" is the largest group.

TABLE 12-6. NUMBER AND RATE OF PATIENTS DISCHARGED FROM SHORT-STAY HOSPITALS, BY AGE AND FIRST-LISTED DIAGNOSIS: UNITED STATES, 1991[a]

First-listed diagnosis	ICD-9-CD code	All ages	Under 15 years	15-44 years	45-64 years	65 years and over	All ages	Under 15 years	15-44 years	45-64 years	65 years and over
		Number of patients discharged in thousands					Rate of patients discharged per 10,000 population				
All conditions		31,098	2,498	11,620	6,173	10,806	1,241.1	453.2	993.4	1,321.6	3,403.1
Diseases of the respiratory system	460-519	3,052	736	500	530	1,286	121.8	133.6	42.7	113.4	405.2
Acute respiratory infections	460-466	518	220	68	75	156	20.7	39.8	5.8	16.0	49.2
Pneumonia	480-486	1,088	214	133	152	589	43.4	38.9	11.4	32.5	185.5
Asthma	493	490	187	128	85	90	19.6	33.9	10.9	18.2	28.5
Diseases of the circulatory system including heart disease	390-459	5,338	28	396	1,509	3,405	213.1	5.1	33.9	323.1	1,072.4
Neoplasms	140-239	2,001	52	363	626	960	79.9	9.5	31.0	133.9	302.3

[a]Discharges from non-Federal hospitals. Excludes newborn infants. Diagnostic groupings and code number inclusions are based on the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CD).

Adapted from National Center for Health Statistics (1993b).

TABLE 12-7. NUMBER OF FIRST-LISTED DIAGNOSES FOR INPATIENTS DISCHARGED FROM SHORT-STAY NON-FEDERAL HOSPITALS, BY ICD-9-CM CODE, AGE OF PATIENT, AND GEOGRAPHIC REGION OF HOSPITAL: UNITED STATES, 1992

First-listed diagnosis	ICD-9-CM code	Total	Age				Region			
			Under 15 years	15-44 years	45-64 years	65 years and over	Northeast	Midwest	South	West
		Number of first-listed diagnoses in thousands								
Diseases of the respiratory system	460-519	2,923	735	460	501	1,227	635	704	1,139	445
Acute Bronchitis	466	251	149	21	23	58	49	64	104	33
Viral Pneumonia	480	39	27	*	*	*	*	12	12	10
Pnuemoccal pneumonia	481	53	6	10	10	27	10	14	17	12
Other bacterial pneumonia	482	202	11	26	31	134	34	47	87	35
Pneumonia, other specified organisms	483	20	*	*	*	8	*	5	8	*
Broncho pneumonia, organism unspecified	485	45	16	*	*	22	9	9	22	5
Pneumonia, organism unspecified	486	700	145	87	108	360	134	177	287	101
Influenza	487	13	*	*	*	6	*	*	*	*
Bronchitis, unspecified	490	23	9	*	6	*	*	*	11	*
Chronic Bronchitis	491	201	*	7	52	141	45	40	86	30
Emphysema	492	29	--	*	8	18	6	8	12	*
Asthma	493	463	193	117	78	76	116	113	152	83

*Figure does not meet standard of reliability or precision.
Adapted from National Center for Health Statistics (1994b).

In the last decade, large increases have occurred in asthma hospitalization rates among the pediatric population. While this pattern has been seen in all age, race and gender groups the most severely affected group is urban black children (Gerstman et al., 1993). This increase was largest among 0 to 4 years old with blacks having approximately 1.8 times the increase of whites (Gergen and Weiss, 1990). During this time, total hospitalization decreased while admissions for lower respiratory tract disease also had a slight decrease (Gergen and Weiss, 1990).

There are differences in the frequency of admission for asthma by age and gender (Skobeloff et al., 1992). Asthma morbidity is known to exhibit seasonal periodicity. For persons ages 5 through 34 years, hospitalization peaked in September through November whereas mortality trends peaked in June through August. For individuals 65-years-old or older, both asthma hospitalization and mortality demonstrated increases during December through February (Weiss, 1990). Crane et al. (1992) states that the most valid and reliable marker of asthma readmission is the number of hospitalization admissions for asthma in the previous 12 mo. In New York City, Carr et al. (1992) found large geographic variations for asthma hospitalization with the highest rate concentrated in the city's poorest neighborhoods. The patients are heavily dependent on hospital outpatient departments and emergency rooms for their ambulatory care. Differences in medical practice styles, reflecting the exercise of physicians discretion in the way illnesses are treated, are important determinants of temporal variation and geographic variation in hospital utilization for many medical conditions.

Storr and Lenney (1989) observed a long term variation in children's hospitalization for asthma and school holidays. The admission rate fell during holidays and there were two or more peaks during terms. The pattern is consistent with a largely viral etiology for asthmatic attacks throughout the year. They postulated that school holidays disrupt the spread of viral infectious in a community, with synchronization of subsequent attacks. Travel during holidays may facilitate acquisition of new viral strains by the community.

Based on a total of 450,000 hospitalizations for asthma and an estimated U.S. population of 10,000,000 asthmatics, the incidence of hospitalization for all asthmatic subjects is about 45 per 1,000 asthmatics (National Institutes of Health, 1991).

Hospital Admission Studies

This section discusses studies of hospital admissions, outpatient visits and emergency room visits, both within the United States and from countries with different medical care systems which may have different medical care practices. Most PM-hospitalization studies consider at least two different classes of admissions. Thus, results of such studies are summarized by class in Tables 12-8 through 12-11.

Bates and Sizto (1983, 1986, 1987) reported results of a study relating hospital admissions in southern Ontario to air pollution levels. Data for 1974, 1976, 1977, and 1978 were discussed in the 1983 paper. The 1985 analyses evaluated data up to 1982 and showed: (1) no relationship between respiratory admissions and $S0_2$ or COHs in the winter; (2) a complex relationship between asthma admissions and temperature in the winter; and (3) a consistent relationship between respiratory admissions (both asthma and nonasthma) in summer and sulfates and ozone, but not to summer COH levels. However, Bates and Sizto note that the data analyses are now complicated by long-term trends in respiratory disease admissions unlikely related to air pollution, but they nevertheless hypothesize that observed effects may be due to a mixture of oxidant and reducing pollutants which produce intensely irritating gases or aerosols in the summer but not in the winter. In a more recent paper, Bates and Sitzo (1987) extend the time period through 1983 and include additional air sampling data not available previously. The monitoring was from 17 air sampling stations and included O_3, sulfate fraction, SO_2, NO_2, and COH. Stepwise multiple regressions confirmed the earlier findings that there was a consistent summer relationship between sulfates and O_3 with hospital admissions. The analyses did not adjust for time trends, trends within the summer season, or serial correlation.

Lipfert and Hammerstrom (1992) conducted a 6-year study of hospital admissions in southern Ontario for 1979 to 1985. Daily hospital admissions were obtained from the Ontario Ministry of Health, the same data base used by Bates and Sitzo (1983, 1986, 1987). The primary focus of the study was on respiratory illness in one of the following ICD codes: 466 acute bronchitis, 480 to 482 or 485 pneumonia, 490 to 492 chronic bronchitis, emphysema, or 493 asthma. Three regions were defined with slightly different air pollution exposures, based on data from the Ontario Ministry of the Environment for SO_2, NO_2, O_3, sulfate fraction, COH, and TSP. Some stations monitored every three or six days and

TABLE 12-8. HOSPITAL ADMISSIONS AND OUTPATIENT VISIT STUDIES FOR RESPIRATORY DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Burnett et al. (1994) All ages in Ontario, Canada, 1983-1988	9 monitoring stations measuring sulfate	sulfate means ranged from 3.1 to 8.2 μg/m^3	108	Lin. regress. on filtered data, 1-d lag best	Ozone	Temperature	none	1.03 (1.02, 1.04)
Thurston et al. (1994a,b) All ages in Ontario, Canada, July and August, 1986-1988	3 monitoring stations measuring sulfate, TSP, and PM_{10}	mean sulfate ranged 38 to 124 (nmole/m^3), PM_{10} 30 to 39 μg/m^3, TSP 62 to 87 μg/m^3	14.4	Linear regression on filtered data, 0-d lag best	Ozone, H+, SO_2, NO_2	Temperature	none	PM_{10} 1.23 (1.02, 1.43)
							ozone	PM_{10} 1.12 (0.88, 1.36)
Thurston et al. (1992) All ages in Buffalo, Albany, New York City, July and August, 1988-1989	3 monitoring stations (one per city) measuring sulfate, H+	(values not given)	Buffalo, 24 Albany, 12, New York, 137	Linear regression on filtered data	Ozone, H+	Temperature	ozone	(not given for PM measures)
Schwartz (1995a) Elderly in New Haven, 1988-1990	PM_{10} monitoring stations averaged, no. of stations not given	mean = 41, 10% tile = 19, 90% tile = 67	8.1	Poisson log-linear regression, 19 day mov. ave. filter, 0-d lag best	Ozone (ppb): mean = 29; 10% tile = 16; 90% tile = 45; SO_2 (ppb): mean = 30; 10% tile = 9; 90% tile = 61	Temperature and dew point adjusted for in the moving average	none	1.06 (1.00, 1.13)
							SO_2 (2 day lag)	1.07 (1.01, 1.14)
Schwartz (1995a) Elderly in Tacoma, 1988-1990	PM_{10} monitoring stations averaged, no. of stations not given	mean = 37, 10% tile = 14, 90% tile = 67	4.2	Poisson log-lin. regress. 19 day mov. ave. filter, 0-d lag best	Ozone (ppb): mean = 25; 10% tile = 13; 90% tile = 36; SO_2 (ppb): mean = 17; 10% tile = 6; 90% tile = 28	Temperature and dew point adjusted for in the moving average	none	1.10 (1.03, 1.17)
							SO_2 (2 day lag)	1.11 (1.02, 1.20)

TABLE 12-8 (cont'd). HOSPITAL ADMISSIONS AND OUTPATIENT VISIT STUDIES FOR RESPIRATORY DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz et al. (1996) Elderly in Cleveland, OH	PM_{10}, O_3, No of sites not given	mean = 43 $\mu g/m^3$	2.2	Generalized additive Poisson model	O_3	temperature, dew point	none	1.06 (1.00, 1.11)
Schwartz (1996) Elderly (≥65) in Spokane, WA	PM_{10}, O_3, No. of sites not given	mean = 46 $\mu g/m^3$	3.9	Generalized additive Poisson model	O_3	temperature, dew point	none	1.08 (1.04 to 1.14)
Schwartz et al. (1993) Asthma visits, <65 age, Seattle, WA	PM_{10} 1 site	mean = 29.6 $\mu g/m^3$ min = 6 max = 103 $\mu g/m^3$	7.1 Asthma	Poisson regression model	SO_2, O_3	temperature	none	1.12 (1.04, 1.2) per 30 $\mu g/m^3$ PM_{10}
Hefflin et al. (1994) Emergency room visits, All ages	PM_{10} 1 site	mean = 40 $\mu g/m^3$ min = 3 max = 1,689 $\mu g/m^3$	13.7 Bronchitis	Poisson regression model (GEE)	None	temperature	none	3.5% per 100 $\mu g/m^3$ PM_{10}
Gordian et al. (1996) Outpatient visits for asthma	PM_{10} 1 site	mean = 45.54 $\mu g/m^3$ min = 5 max = 565 $\mu g/m^3$	2.12 Asthma	Poisson multiple regression model	CO	temperature	CO	2.5% ↑ per 10 $\mu g/m^3$ PM_{10}

*Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

TABLE 12-9. HOSPITAL ADMISSIONS STUDIES FOR COPD

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Sunyer et al. (1993) Adults in Barcelona, 1985-1989	15 monitoring stations measuring black smoke	winter 33% tile = 49, 67% tile = 77, summer 33% tile = 36, 67% tile = 55	12	Autoregressive linear regression analysis, 0-d lag best	Sulfur dioxide, winter 33% tile = 49 $\mu g/m^3$, 67% tile = 77, summer 33% tile = 36, 67% tile = 55	min temp, dummies for day of week and year	none SO_2	winter: 1.15 (1.09, 1.21) summer: 1.05 (0.98, 1.12) winter: 1.05 (1.01, 1.09) summer: 1.01 (0.97, 1.05)
Schwartz (1994e) Elderly in Birmingham, 1986-1989	1 to 3 monitoring stations measuring PM_{10}	mean = 45, 10% tile = 19 90% tile - 77	2.2	Autoregressive Poisson model, 0-d lag best	Ozone, mean = 25 ppb, 10% tile = 14, 90% tile = 37	7 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.13 (1.04, 1.22)
Schwartz (1994f) Elderly in Minneapolis, 1986-1989	6 monitoring stations measuring PM_{10}	mean = 36, 10% 2.2 tile = 18, 90% tile = 58	2.2	Autoregressive Poisson model, 1-d lag best	Ozone, mean = 26 ppb, 10% tile = 11, 90% tile = 41	8 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.25 (1.10, 1.44)
Schwartz (1996) Elderly (>65) in Spokane, WA	No of sites not given, PM_{10}, O_3	mean = 46 $\mu g/m^3$	3.9	Generalized additive Poisson model	O_3	temperature, dew point	none	1.17 (1.08, 1.27)
Schwartz (1994d) Elderly in Detroit 1986-1989	2 to 11 PM_{10} mon. stations, data for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	15.7	Poisson auto-regress. mod. using GEE, 0-d lag best	Ozone: mean 21 ppb; 10% tile 7: 90% tile 36	Dummy variables ozone for temp, month, lin. & quad. time trend	none	1.10 (1.02, 1.17)

*Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

TABLE 12-10. HOSPITAL ADMISSIONS STUDIES FOR PNEUMONIA

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz (1994f) Elderly in Minneapolis, 1986-1989	6 monitoring stations measuring PM_{10}	mean = 36, 10% tile = 18, 90% tile = 58	6.0	Autoregressive Poisson mod., 1-d lag best	Ozone, mean 26 ppb; 10% tile 11; 90% tile 41	8 categories of temp. & dew pt., month, year, lin. & quad. time trend	none	1.08 (1.01, 1.15)
Schwartz (1994e) Elderly in Birmingham, 1986-1989	1 to 3 monitoring stations measuring PM_{10}	mean = 45, 10% tile = 19, 90% tile = 77	5.9	Autoregressive Poisson modl, 0-d lab best	Ozone, mean 25 ppb; 10% tile 14; 90% tile 37	7 cat. of temp. & none dew pt., month, year, lin. & quad. time trend	none	1.09 (1.03, 1.15)
Schwartz (1994d) Elderly in Detroit 1986-1989	2 to 11 PM_{10} mon. stations, data for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	15.7	Poisson autoregress. mod. using GEE, 0-d lag best	Ozone, mean 21 ppb; 10% tile 7; 90% tile 36	Dummy variables ozone for temp, month, lin. & quad. time trend	ozone	1.06 (1.02, 1.10)
Schwartz (1996) Elderly ($\geq$65) in Spokane, WA	PM_{10}, O_3, No. sites not given	mean = 46 $\mu g/m_3$	3.9	Generalized additive Poisson model	Ozone	temperature, dew point	none	1.06 (0.98, 1.13)
Schwartz (1994g) Elderly in Philadelphia	No. of sites not given TSP, O_3, SO_2	not given	not given	Generalized additive Poisson model	Ozone, SO_2	temperature, dew point	none	1.22 (1.10, 1.36)

*Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

TABLE 12-11. HOSPITAL ADMISSIONS STUDIES FOR HEART DISEASE

Study	PM Type & No. Sites	PM Mean & Range	Ave. Count per Day	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Result* (Confidence Interval)
Schwartz and Morris (1995) Elderly in Detroit 1986-1989 Ischemic Heart Disease	2 to 11 PM_{10} monitoring stations, data available for 82% of possible days	mean = 48, 10% tile = 22, 90% tile = 82	44.1	Poisson auto-regressive model using GEE, 0-d lag best	SO_2, mean = 25 ppb, 10% tile = 11, 90% tile = 44 CO, mean 2.4 ppm, 10% tile 1.2, 90% tile = 3.8	Dummy vars. for temp, month, lin. & quad. time trend	none	1.018 (1.005, 1.032)
							ozone, CO, SO_2	1.016 (1.002, 1.030)
Burnett et al. (1995) All ages in Ontario, Canada, 1983-1988 Cardiac disease admission	22 sulfate monitoring stations	station means ranged from 3.0 to 7.7 in the summer and 2.0 and 4.7 in the winter	14.4	Linear regression on a 19 day linear filter, 1-d lag best	Ozone averaged 36 ppb	Temperature included in separate analyses by summer and winter	none	1.03 (1.02, 1.04)
							ozone	1.03 (1.02, 1.05)

*Relative risk calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

averages were taken by region for those monitors present. A Box-Jenkins ARIMA multiple regression model was used to analyze the data. Bivariate correlations were calculated between the pollutants and respiratory illness. Stepwise multiple regressions did not include TSP as a significant factor, but O_3 was significant for January and February and SO_2 was significant for some regions in July and August.

Burnett et al. (1994) studied hospital admissions in southern Ontario, using a broader area than that used by Bates and Sitzo (1983, 1986, 1987). The respiratory admissions were for 1983 to 1988 and were restricted to the ICD9 codes of 466, 480 to 486, 490 to 494, and 496. The non respiratory control admissions included the codes of 280 to 281.9, 345 to 347, 350 to 356, 358 to 359.5, 530 to 534, 540 to 543, 560 to 569, 571, 572, 574 to 578, 594, and 600. Twenty-two monitoring stations were used to estimate daily O_3 and sulfate fraction data; meteorological data came from 10 different stations. The daily fluctuations in admissions were related to the pollution and meteorological data after subtracting a 19 term linear trend as discussed by Shumway et al. (1983). The rates were analyzed using a random effects model, where hospitals were assumed to be random. The estimates were obtained using the generalized estimating equations (GEE) of Liang and Zeger (1986). In general, O_3, sulfate fraction, and temperature were all predictors of hospital admissions; but O_3 tended to be more significant than did sulfate fraction. The models predicted about a 3% increase in respiratory hospital admissions for about a 14 $\mu g/m^3$ concentration of sulfate fraction.

Thurston et al. (1994b) studied hospital admissions in the Toronto metropolitan area. during the months of July and August of 1986, 1987, 1988 and restricted to the following causes: total respiratory (ICD9 codes 466, 480, 481, 482, 485, 490 to 493), asthma (493), and non respiratory control (365, 430, 431, 432, 434, 435, 531, 543, 553.3, 537, 540, 541, 542, 543, 590). There were no stated restrictions on age. Pollution data consisted of acidity (H^+) and sulfate data measured at three sites during the three summer seasons. In addition, O_3, NO_2, and SO_2 and daily 24-h $PM_{2.5}$ and PM_{10} were measured at several other stations. Meteorological measurements were available from two of the monitoring sites. Ordinary least squares analyses were calculated after the environmental variables were detrended. The data for the three summers were combined. In general, O_3 was the strongest predictor of hospital admissions above the strong effect of temperature. There was some suggestion of an effect from PM_{10},

especially for total respiratory admissions. There were strong associations with H^+ and with $SO_4^=$. Non-linear temperature terms were not fitted.

Sunyer et al. (1991, 1993) studied daily emergency room admissions for COPD in adults in Barcelona, Spain. The original study included admissions for the years 1985 and 1986. A specially trained physician collected data from clinical records from the four largest hospitals in Barcelona. A panel of chest physicians defined expressions used to determine the diagnosis of COPD. Seventeen manual samplers and two automatic samplers took 24-h measurements of SO_2, black smoke, CO and O_3. Neither SO_2 nor black smoke exceeded the European Community standards. A Box-Jenkins ARIMA (auto-regressive integrated moving average) time series model was used to analyze the results. COPD was found to be related to SO_2, black smoke, and CO. The relationship with black smoke was especially pronounced for temperatures greater than 11.7° C. In the later paper, Sunyer et al. (1993) included the larger time period of 1985 to 1989. The study was restricted to individuals in the four largest hospitals at least 14 years of age. Fifteen manual samplers provided SO_2 and black smoke measurements. Ridge regression (a modification of standard multiple linear regression) was used to analyze the daily admissions, but the analyses were done separately by season. Ridge regression is a conservative method of handling collinear variables, but it does not take into account the effects of non-normality of counts. Lag variables to adjust for the autocorrelation were selected according to the methodology of Box and Jenkins (1976). Significant changes in admissions were found for both SO_2 and black smoke for the winter season, but only SO_2 was significant in the summer.

Hospital admissions for all hospitals in the Birmingham, AL, SMSA were studied by Schwartz (1994e). The admissions were restricted to pneumonia (ICD-9 codes 480 to 487) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490 to 496) from January 1, 1986 to December 31, 1989. Only persons age 65 were included in the analysis. Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Birmingham stations reporting on a given day. The author used three different models for the analysis including (1) Fourier series adjustments for season with linear and quadratic terms for temperature, dew point, and time trend, (2) a similar model with cubic splines used instead of Fourier series, and (3) a nonparametric approach. Serial correlation was adjusted for using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The relative risk of pneumonia was found to be about 1.16 (1.05 to 1.28) corresponding to an

increase of 100 $\mu g/m^3$ of PM_{10}. The relative risk of COPD was found to be about 1.24 (1.05 to 1.45) for an increase of 100 $\mu g/m^3$ of PM_{10}. Associations with O_3 were found to be slightly weaker.

Schwartz (1994d) also studied hospital admissions for the elderly in Detroit, restricted to pneumonia (ICD-9 codes 480 to 486) and chronic obstructive pulmonary disease (COPD) (ICD-9 codes 490 to 496) from January 1, 1986 to December 31, 1989. Only persons age 65 or older were included in the analysis. Separate counts were constructed for asthma (493) and all other COPD (491 to 492 and 494 to 496). Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Detroit metropolitan area stations reporting on a given day. The author used three different approaches to the analysis, including a nonparametric approach. Serial correlation was adjusted for using autoregressive terms which were estimated using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The estimated relative risk coefficient for pneumonia was 1.012 (1.004 to 1.019) for an increase of 10 $\mu g/m^3$ of PM_{10}. The estimated relative risk for COPD was 1.020 (1.004 to 1.032) for an increase of 10 $\mu g/m^3$ of PM_{10}. Associations with O_3 were also found, but the dose response relationship was not as consistent.

Hospital admissions for all hospitals in Spokane, WA, were also studied by Schwartz (1996). The admissions were restricted to respiratory disease (ICD-9 codes 460 to 519) from January 1, 1988 to December 31, 1990. Only individuals $\geq$ 65 yrs were included in the analysis. Daily pollution estimates of PM_{10} and O_3 were computed by averaging all Spokane stations reporting on a given day. PM_{10} values averaged 46 $\mu g/m^3$ with 10 and 90 percentile values of 16 and 83 $\mu g/m^3$. Monitoring for SO_2 in Spokane from January to April 1985 yielded an average SO_2 concentration of 0.0037 ppm. The author used three different models for the analysis, including (1) Fourier series adjustments for season with linear and quadratic terms for temperature, dew point, and time trend, (2) a similar model with cubic splines used instead of Fourier series, and (3) a nonparametric approach. Serial correlation was adjusted for using the generalized estimating equations of Liang and Zeger (1986). The various models gave reasonably similar results. The relative risk of respiratory disease was about 1.08 (1.04 to 1.14) corresponding to an increase of 50 $\mu g/m^3$ of PM_{10}. Associations were also found with O_3, giving a relative risk of 1.24 (1.00 to 1.54) for an increase of 50 $\mu g/m^3$. Inclusion of both pollutants in the model had little effect on either estimate.

Pönkä and Virtanen (1994) studied hospital admissions for exacerbations of chronic bronchitis (ICD-9 code 491) and emphysema (ICD-9 code 492) in Helsinki, Finland during 1987 to 1989. Individuals with the diagnosis of asthma (ICD9 code 493) were excluded. Sulfur dioxide was measured hourly at four stations, NO_2 at two stations, and O_3 at one station; TSP was measured every other day at four stations and every third day at two stations. Meteorological information was available from a single station but the location was not specified. Daily admissions were analyzed using Poisson regression as described by McCullagh and Nelder (1989). The model included variables for season, day of week, year, and influenza epidemics. The authors report that the day of week variables effectively reduced the autocorrelation, and so autocorrelation terms were not included due to their difficulty of interpretation. For persons <65 years old, the only effects seen were with SO_2 on the same day or three days previous. For individuals older than age 64, the only effect seen was for NO_2 six days previous. Although these results are difficult to interpret, the study did not find any results suggesting a PM effect.

Pönkä (1991) also studied hospital admissions for asthma (ICD9 code 493) in Helsinki during 1987 to 1989. Persons with the diagnosis of bronchiolitis were excluded. Sulfur dioxide was measured hourly at four stations, NO_2 at two and O_3 at one; TSP was measured every other day at four stations and every third day at two. Meteorological information was available from a single station. The analysis was done using simple and partial age specific correlations of asthma admissions with mean daily concentrations of SO_2, NO_2, NO, CO, TSP, O_3, temperature, wind speed and humidity. No adjustment was made for season or serial correlation. TSP was found to be significantly correlated with hospital admissions, but was less correlated than some of the other pollutants.

White et al. (1994) studied asthma outpatient clinic visits of children at Grady Memorial Hospital in Atlanta. The encounter forms for each child between June 1, 1990 and August 31, 1990 were abstracted, excluding visits when pneumonia or bronchiolitis was mentioned. Hourly O_3 measurements were available from two stations in the area. PM_{10} data were available from the middle of July, but data before that time had to be estimated using visibility data from Hartsfield International Airport. Clinic visits were increased when O_3 exceeded 0.11 ppm. Using a Poisson regression model, the estimated increase, as measured by a rate ratio, was 1.02 (CI = 0.96, 1.13) for a 10 $\mu g/m^3$ increase in PM_{10}.

Tseng et al. (1992) studied quarterly hospital discharges for asthma (ICD-9 Code 493) from the computerized hospital inpatient data base of the Medical and Health Department of Hong Kong. The study ran from the second quarter of 1983 to the last quarter of 1989. The discharges were split into four groups: under age 1, age 1 to 4, age 5 to 14, and adult. Quarterly averages of SO_2, NO_2, O_3, TSP and RSP values were obtained from the environmental protection unit of the Hong Kong Government. Multiple regression analyses were performed on the hospitalization rates using the four different age groups as the dependent variables and the pollution values as the independent values. Season and year were used as covariates, but no meteorological variables were included in the analyses. The significant correlations were between TSP and hospitalization rates for children aged 1 to 4 and children aged 5 to 14. The correlations for RSP tended to be similar, but smaller in magnitude.

Asthmatic admissions and emergency room visits to the Pediatric Department of the Hospital de S. Joäo (serving the Oporto area of Portugal) during the period from 1983 to 1987 were studied by Queirós et al. (1990). Air pollution was estimated from measurements of SO_2 and black smoke (BS) taken daily at four stations. The admissions were adjusted so that the values represented deviations from the average for a particular month or year. No correlation was found between daily, monthly, or quarterly mean admissions or visits and BS levels but SO_2 levels were correlated with monthly mean admissions. The authors concluded that there was no evidence for PM pollution effects on admissions or visits.

During January 1985, large parts of Europe from western Germany to Great Britain experienced a pollution event traced to emission sources in Central Europe. This event was tracked by monitoring stations in several countries as it moved from east to west, and then finally dissipated over the North Sea. Very high levels of PM, SO_2, and NO_x were reported. Wichmann et al. (1989) studied mortality, hospital admissions, ambulance transports and outpatient visits for respiratory and cardiovascular disease in West Germany during the 1985 event. During that time, daily suspended particulate matter reached 600 μg/m, SO_2 reached 830 $\mu g/m^3$, and NO_2 reached 410 $\mu g/m^3$. Total mortality rose immediately with the increase in pollution (January 16, 1985), and reached a maximum on January 18. The increase in mortality was about 8 percent. Similarly, increases in hospital admissions (15 percent), outpatient visits (12 percent), and ambulance transports (28 percent) were seen. Wichmann et al. (1988a,b)

reported on other events in 1986 and 1987 which related lung function changes to SO_2 levels but did not report PM data.

Walters et al. (1994) studied hospital admissions in Birmingham, England. The admissions were restricted to asthma or acute respiratory disease (ICD9 codes of 466, 480 to 486, and 490 to 496) for the period of April 1988 to March 1990. No age restrictions were indicated. Seven monitoring stations were used to estimate BS and SO_2 levels. Meteorological information came from the University of Birmingham Department of Geography. The data were divided into four seasons for analysis to control for seasonal variation in all variables. Stepwise multiple regression models were fitted to the hospital admissions data using pollution and meteorological variables as independent variables. Marginally significant regression coefficients were found for both pollutants for both endpoints, especially in the winter season. Additional analyses were run using 2-day lags of the pollution variables, and some of these were marginally significant. This study adds little to the effect of particulate matter on respiratory hospital admissions because of the difficulties in comparing black smoke to particulate fractions.

In another study, Schwartz et al. (1993), emergency room visits for 8 hospitals in the greater Seattle area were abstracted for the period September 1, 1989 to September 30, 1990. Asthma was defined as a diagnosis of ICD9 Codes 493, 493.01, 493.10, 493.90 and 493.91. Sulfur dioxide was measured at an industrial site, PM_{10} was available from a residential area north of town, and O_3 was measured at a site 20 km east of town. Poisson regression as described by McCullagh and Nelder (1983) was used to estimate the effect of pollution on asthma visits with adjustments for serial correlation using the method of Zeger and Liang (1986). Logistic regression coefficient estimated from the Poisson regression gave a values of .0036 (.0012) for PM_{10}. The pollution monitors were located far from the study population, but the analyses of partial data suggested that the station produced estimates that were highly correlated with the local data.

Urgent hospital admissions for respiratory illnesses in Montreal, Canada were collected from 14 hospitals from 1984 to 1988, and were split into asthma and non-asthma admissions (Delfino et al., 1994a,b). The definitions were similar to those used by Bates and Sitzo (1987). City-wide averages of O_3, PM_{10}, and sulfate fraction were calculated from seven selected monitoring stations. PM_{10} was measured every sixth day, and values for the other five days were estimated. A high-pass filter was used to eliminate yearly seasonal trends (see Shumway et al.,

1983). Weather variables included temperature and humidity. Regression analyses with and without autoregressive terms found few significant relationships between the health endpoints and the various pollutants.

Duclos et al. (1990) studied hospital admissions for respiratory and non-respiratory conditions during several forest fires in northern California. The fires commenced on August 30, 1987, and TSP levels increase to about 300 $\mu g/m^3$ from a background level generally below 100 $\mu g/m^3$. The analysis consisted of comparing observed versus expected rates without adjustment for serial correlation or other factors. Although there was a significant increase in visits for respiratory conditions, the same pattern appeared for visits for injuries.

Pope (1991, 1989) studied hospital admissions in the Salt Lake Basin during the period surrounding the shut-down or strike of the steel mill. According to Pope (1991), PM_{10} pollution in the Utah Valley came from many sources, but the primary source was a 45-year-old integrated steel mill with coke ovens, blast furnaces, open hearth furnaces, and a sintering plant. When in operation, the mill emitted 82 to 92% of the valley's industrial PM_{10} pollution and 50 to 70% of the total Utah Valley PM_{10} emissions. The steel mill shut down from August 1, 1986 to September 1, 1987. Winter PM_{10} levels were approximately twice as high when the mill was open compared to when it was closed. Three mountain areas of central and north central Utah were monitored for admissions to three local hospitals. Daily admissions for asthma, bronchitis, and pneumonia were recorded. PM_{10}, SO_2, and NO_2 levels were monitored at a site 5 km northeast of the steel mill. Admissions for bronchitis and asthma were higher during periods of operation of the steel mill when compared to other areas of Utah. Logistic regressions were generally not significant, but respiratory hospital admissions were associated with monthly mean PM_{10} levels.

Lamm et al. (1994) reanalyzed the data of Pope (1991, 1989). This new analysis attempted to investigate a possible viral cause of the illnesses. Monthly respiratory syncytial virus (RSV) activity was measured in terms of total monthly bronchiolitis admissions in all IHC hospitals in Utah and Salt Lake counties. Section 12.3.2.2 provides some background on RSV and childhood respiratory illness. When this variable measured as described (total monthly bronchiolitis), was included in the analysis, the significance of the effect of PM was eliminated.

Hefflin et al. (1994) compared the number of emergency room visits in southeast Washington state for twelve respiratory disorders for each day of 1991 with daily PM_{10} levels.

During two dust storms on October 16 and 21, 1991 PM_{10} reached 1,689 and 1,035 $\mu g/m^3$, respectively. Other pollutants were not measured. Airborne particles in rural eastern Washington, which are mainly volcanic in origin, fall mostly in the PM_{10} fraction and belong to the plagioclase (glass) mineral class of aluminum silicates and other oxides. The authors used a Poisson regression model to predict daily emergency room visits as a function of season, relative humidity, and one and 2-day lags of PM_{10} pollution. Variances were estimated using the generalized estimating equations with an exchangeable correlation structure as described by Liang and Zeger (1986). Daily emergency room totals for each disorder, except respiratory allergy, had a statistically significant inverse correlation with mean daily temperature. The maximum observed/ expected ratio for respiratory disorders from the dust storms on October 16 and 21 was 1.2. The author considered this relatively low ratio for such high pollution days as indicating that the high PM_{10} levels probably had a minimal public health impact. A statistically significant relationship between a year of daily PM_{10} levels for emergency room visits for bronchitis and sinusitis was found, although the estimated regression coefficient indicated a small effect. Ten other disorders, including asthma, pneumonic influenza, and COPD did not show this relationship.

Gordian et al. (1995, 1996) examined associations between daily PM_{10}, temperature measurements and daily outpatient visits for respiratory disease including asthma, bronchitis and upper respiratory conditions. The study was done in Anchorage, Alaska, where there was no industrial source of air pollution, so that PM_{10} contains primarily earth crustal material and volcanic ash. Outpatient visits were obtained from insurance claims for state and municipal cmployees and their dependents covered by Aetna insurance during the time period May 1, 1992 to March 1, 1994. The numbers of visits were modeled using a weighted 19-day moving average filter (see Kinney and Ozkaynak, 1991) to adjust for long term cycles including season. The results showed that an increase of 10 $\mu g/m^3$ in PM_{10} results in a 2.5% increase in asthma visits and a 1.2% increase in visits for upper respiratory illness. PM_{10} levels ranged from 5 to 565 $\mu g/m^3$ with a mean of 46 $\mu g/m^3$.

Thurston et al. (1992) studied hospital admissions for respiratory disease among all ages in Buffalo, Albany, and New York City during July and August, 1988-1989. Three monitoring stations (one per city) measured sulfate, H+, and ozone. A linear regression analysis on filtered

data showed relative risk of 1.05 (1.01, 1.10) for sulfate. Positive results for H^+ are discussed in detail in Section 12.5.

Schwartz (1994f) studied hospital admissions for elderly patients in Minneapolis during 1986 to 1989. Exposure measurements were obtained from 6 monitoring stations which measured PM_{10} and O_3. The mean PM_{10} value was 36 $\mu g/m^3$, the 10th percentile was 18 and the 90th was 58. The mean O_3 value was 26 ppb, the 10th percentile was 11 and the 90th was 41. An autoregressive Poisson model with 8 categories of temperature and dew point, month, year, linear and quadratic time trend was used to analyze the data. The estimated relative risk for a 100 $\mu g/m^3$ increase in PM_{10} was 1.57 (1.20, 2.06) for COPD (ICD9 490 to 496) and 1.17 (1.02, 1.33) for pneumonia (ICD9-480 to 487).

Schwartz (1994g) studied hospital admissions for pneumonia for individuals age 65 or older in Philadelphia, PA. Daily pollution estimates of TSP, SO_2, and O_3 were computed by averaging all Philadelphia stations reporting on a given day. The author used a generalized additive Poisson model including Fourier series adjustments for season, linear and quadratic terms for temperature, dew point, and time trend. The relative risk of pneumonia was found to be about 1.22 (1.10 to 1.36) corresponding to an increase of 100 $\mu g/m^3$ of TSP. Associations with SO_2 and O_3 were also significant.

Schwartz et al. (1996b) studied hospital admissions for all respiratory disease for individuals age 65 or older in Cleveland, OH. Daily pollution estimates of PM_{10} and ozone were computed by averaging all Cleveland stations reporting on a given day. The authors used a generalized additive Poisson model including Fourier series adjustments for season, linear and quadratic terms for temperature, dew point, and time trend. The relative risk of respiratory disease was found to be about 1.12 (1.01 to 1.24) corresponding to an increase of 100 $\mu g/m^3$ of PM_{10}. Associations with ozone were also found to be significant.

Schwartz (1995a) studied respiratory hospital admissions (ICD9-460-519) for elderly patients in New Haven and Tacoma during 1988 to 1990. For New Haven, daily PM_{10} exposure estimates were averaged from all monitoring stations giving data. The mean PM_{10} was 41, the 10th percentile 19 and the 90th percentile 67 $\mu g/m^3$. The mean O_3 was 29, the 10th percentile, and the 90th percentile 45 ppb. The mean SO_2 was 30 ppb, the 10th percentile 9 and the 90th percentile 61. A Poisson log-linear regression model with a 19 day moving average filter was used to analyze the data. Temperature and dew point were adjusted for in the moving average.

The relative risk for respiratory hospital admissions for a 50 μg/m^3 increase in PM_{10} was 1.06 (1.00, 1.13). Using a two day lag SO_2 term in the model, the RR was 1.07 (1.01, 1.14). The same analysis was run for the Tacoma data. The RR for respiratory hospital admissions for a 50 μg/m^3 increase in PM_{10} was 1.10 (1.03, 1.17). Using a two day lag SO_2 term in the model, the RR was 1.11 (1.02,1.20).

Schwartz and Morris (1995) studied ischemic heart disease hospital admissions (ICD9 410 to 414, 427 and 428) for the elderly in Detroit from 1986 to 1989. There were from 2 to 11 PM_{10} monitoring stations operating during the study period, and data were available for 82% of possible days The mean PM_{10} was 48 μg/m^3, the 10th percentile 22 and the 90th percentile 82. The mean SO_2 was 25 ppb, the 10th percentile 11 and the 90th percentile 44. A Poisson auto-regressive model using GEE was used to analyze the data with dummy variables for temperature, month, and linear and quadratic time trend. The relative risk ratio for hospital admissions for ischemic heart disease for a 32 μg/m^3 increase in PM_{10} was 1.018 (1.005, 1.032). Using O_3, CO and SO_2 in the model resulted in a relative risk of 1.016 (1.002, 1.030).

Cardiac and respiratory hospital admissions in 168 acute care hospitals in Ontario, Canada for 1983 to 1988 calendar years were studied by Burnett et al. (1995). The cardiac admissions were defined as ICD9 codes 410, 413, 427, and 428, and the respiratory admissions as codes 466, 480 to 486, 490 to 494 and 496. No other age restrictions were given. Twenty-two monitoring stations were used to estimate daily O_3 and sulfate fraction data. Meteorological information came from 10 different stations. The daily fluctuations in admissions were related to the pollution and meteorological data after subtracting a 19 term linear trend as discussed by Shumway et al. (1983). The rates were analyzed using a random effects model, where hospitals were assumed to be random. The estimates were obtained using the generalized estimating equations (GEE) of Liang and Zeger (1986). The sulfate fraction, O_3, and temperature were all predictors of hospital admissions, with O_3 more significant than the sulfate fraction. The models tended to predict about a 3 to 4% increase in respiratory admissions and about a 2 to 3% increase in cardiac admissions with about a 13 μg/m^3 increase in the concentration of sulfate fraction.

Hospital Admission Studies Summary

Hospitalization data can provide a measure of the morbidity status of a community during a specified time frame. Hospitalization data specific for respiratory illness diagnoses, or more

specifically for COPD and pneumonia, provide an index of respiratory status. Such studies provide an outcome measure that relates to mortality studies for total and specified respiratory measures as were summarized earlier in Tables 12-8 through 12-11. The separate panels in Figure 12-1 compare the studies by their relative risk (along with 95% confidence intervals). Many of the same factors and concerns related to the mortality studies are at issue for these studies also.

Both COPD and pneumonia hospitalization studies show moderate but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The admission studies of respiratory disease show a similar effect. The hospitalization studies in general use similar analysis methodologies, and the majority of the COPD and pneumonia papers are written by a single author. There is a suggestion of a relationship to heart disease, but the results are based on only two studies and the estimated effects are smaller than those for other endpoints. Overall, these studies are indicative of morbidity effects being related to PM. They are also supportive of the mortality findings, especially with the more specific diagnosis relationships.

While a substantive number of hospitalizations for respiratory related illnesses occur in those $\geq$65 years of age, there are also numerous hospitalizations for those under 65 years of age. Several of the hospitalization studies restricted their analysis by age of the individuals. These studies are indicative of health outcomes related to PM for individuals $\geq$65 years of age, but did not examine other age groups that would allow directly comparable estimates as some mortality studies did. The limited analyses examining young age groups, especially children $\leq$14 years of age constrain possible conclusions about this age group.

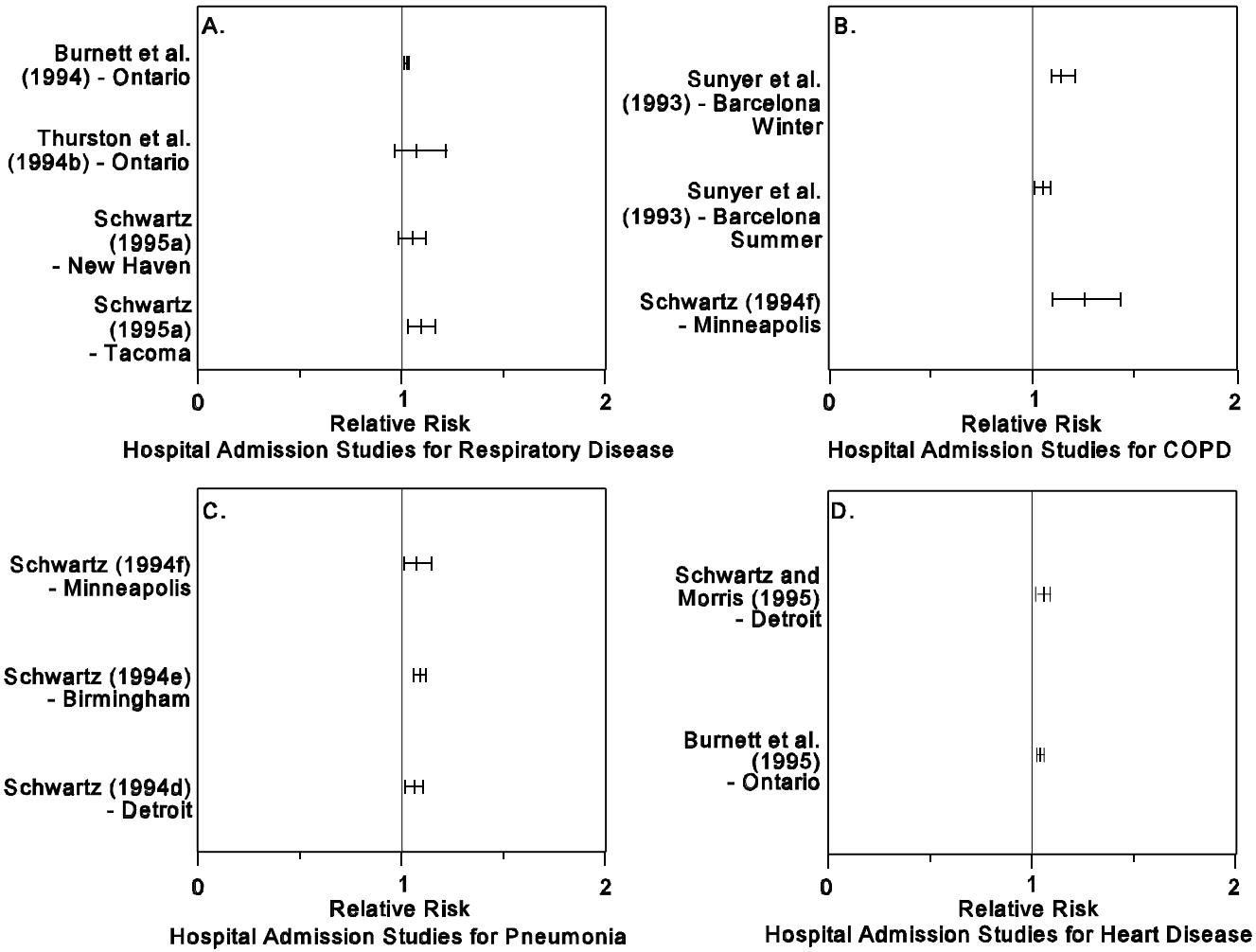

Figure 12-1. Relative risk for hospital admission for respiratory diseases, Chronic Obstructive Pulmonary Disease (COPD), pneumonia, and heart disease for a 50 $\mu g/m^3$ increase in PM_{10} (or equivalent) as shown for several studies.

Schwartz (1995b) reviewed the hospital admission and mortality studies of particulate matter and ozone. The hospitalization results were based on the studies of Thurston et al., (1992), Schwartz (1994e), Burnett et al. (1994), Schwartz (1994f), Sunyer et al. (1993), Schwartz (1994d), and Burnett et al. (1995). Summary tables in Schwartz (1995b) for all respiratory admissions showed relative risks ranging from 1.10 to 1.20 per 100 $\mu g/m^3$ TSP (or equivalently, 1.05 to 1.10 per 50 $\mu g/m^3$ PM_{10}). Summary tables for COPD admissions showed relative risks ranging from 1.15 to 1.57 per 100 $\mu g/m^3$ TSP (or equivalently, 1.07 to 1.25 per 50 $\mu g/m^3$ PM_{10}). Schwartz (1996b) argues that because there is no significant heterogeneity in the relative risks across studies that:

> "This suggests that confounding by other pollutants or weather is not the source of these associations, since the coincident weather patterns and levels of other pollutants varied greatly across the studies. In particular, studies in the western United States (Spokane, Tacoma) had very low levels of sulfur dioxide, and much less humidity than [sic] in the eastern United States locations."

However, tests for homogeneity are known to have very little power against specific alternatives, and so this conclusion may not be appropriate (Hunter and Schmidt, 1989). Even when SO_2 levels are low, anthropogenic PM from combustion or industrial emissions may be accompanied by other criteria pollutants such as CO, O_3, or NO_x.

Air Quality Criteria for Ozone and Other Photochemical Oxidants (U.S. Environmental Protection Agency, 1996) examines several of these same studies for an O_3 effect and concludes that collectively the studies (Thurston et al., 1992, 1994b; Burnett et al., 1994; Delfino et al., 1994a; Schwartz, 1994e,d,f) indicate that ambient O_3 often has a significant effect on hospital admission for respiratory causes with a relative risk ranging from 1.1 to 1.36/100 ppb O_3. Schwartz (1995b) reports a range of 1.04 to 1.54/100 mg/m^3 O_3 and notes that these results are from two pollutant models (PM and O_3) and, while the RR for O_3 are somewhat lower than PM, the same pattern of a larger RR for COPD compared to all respiratory admissions is observed. Also, Schwartz (1995a) in New Haven and Tacoma stated that two pollutant models were examined to determine which pollutant made independent contributions to explaining respiratory hospital admission. The PM_{10} and O_3 associations appeared to be independent of each other, with no reduction in the relative risk for one pollutant after control for the other. Additionally, while there is a suggestion of an effect for PM and heart disease, none was reported for O_3.

The hospitalization studies usually compared daily fluctuations in admissions about a long term (e.g., 19 day) moving average. These fluctuations were regressed on PM estimates for the time period immediately preceding or concurrent with the admissions. Some authors considered lags up to 5 days, but the best predictor usually was the most recent exposure. Some morbidity outcomes associated with hospitalization may be appropriately associated with concurrent admission, while others may require several days of progression to end in an admission. Exposure-response lag periods are not yet well examined for hospital admissions related to PM exposures.

12.3.2.2 Respiratory Illness Studies

Respiratory illness and the factors determining its occurrence and severity are important public health concerns. This section discusses epidemiologic findings relating estimates of PM exposure to respiratory illness. This effect is of public health importance because of the widespread potential for exposure to PM and because the occurrence of respiratory illness is common (Samet et al., 1983; Samet and Utell, 1990). Of added importance is the fact that recurrent childhood respiratory illness may be a risk factor for later susceptibility to lung damage (Glezen, 1989; Samet et al., 1983; Gold et al., 1989).

The PM studies generally used several different standard respiratory questionnaires that evaluated respiratory health by asking questions about each child's and adult's respiratory disease and symptom experience daily, weekly or over a longer recall period. The reported symptoms and diseases characterize respiratory morbidity in the cohorts studied. A brief discussion of aspects of epidemiology of respiratory morbidity provides a background for studies examining PM exposure in relation to respiratory health. Respiratory morbidity typically includes specific diseases such as asthma and bronchitis, and broader syndromes such as upper and lower respiratory illnesses.

Asthma is characterized by reversible airway obstruction, airway inflammation, and increased airway responsiveness to non-specific stimuli (National Institutes of Health, 1991). Asthma patients develop clinical symptoms such as wheezing and dyspnea after exposure to allergens, environmental irritants, viral infections, cold air, or exercise. Exacerbations of asthma are acute or subacute episodes of progressively worsening shortness of breath, cough, wheezing, chest tightness, or some combination of these symptoms associated with decreased levels of

various measures of forced expiratory volume. Although viral respiratory tract infections are common asthma triggers, especially in young children (National Institutes of Health, 1991), symptoms such as wheezing may occur without an infectious cause.

Overall, an estimated 4.9% of the total U.S. population or over 12 million people, have asthma (National Center for Health Statistics, 1994c). The prevalence of physicians diagnosed asthma among children under age 18 is 6.3/100 (National Center for Health Statistics, 1994c). From 1982 through 1992, asthma mortality among persons aged 5 to 34 years (for whom the diagnosis is likely most accurate) increased 42%, from 3.4 per 1 million population (401 deaths) to 4.9 per 1 million population (569 deaths) (U.S. Centers for Disease Control, 1995).

Chronic bronchitis in adults is defined as a clinical disorder characterized by excessive mucous secretion in the bronchial tubes with an associated chronic productive cough on most days for a minimum of 3 months of the year for not less than 2 successive years (American Thoracic Society, 1962). Chronic mucus hypersecretion can occur with or without obstruction. When the obstruction is fixed, there is often associated emphysema. The diagnosis can only be made after excluding other disorders with similar symptoms. Symptoms and findings observed in children with physician-diagnosed chronic bronchitis commonly include recurrent respiratory infections and wheezing, with chronic phlegm production and chronic cough being less prevalent (Burrows and Lebowitz, 1975). Respiratory syncytial virus (RSV) and parainfluenza virus are isolated in cases of bronchitis (Chanock and Parrott, 1965), but symptoms of bronchitis may occur without an infectious cause.

Viral respiratory illnesses can be subdivided by predominant anatomic site of involvement in the respiratory tract: rhinitis (the common cold), pharyngitis, laryngitis, laryngotracheo bronchitis (croup), tracheobronchitis, bronchiolitis, and pneumonia. In many instances, signs and symptoms referable to more than one site (e.g., pharyngitis, laryngitis, and rhinitis) may occur at the same time in the same patient.

Rhinoviruses lead the list as the most common group of viruses that cause acute upper respiratory illness (URI) in adults and children. Other common viruses include coronaviruses, parainfluenza virus, respiratory syncytial virus, and influenza virus. The number of URI acquired per year decreases with age. Infants and preschool children have the highest incidence (4 to 8 colds per year), and adults generally have two to five colds per year. Typically, symptoms and responses on respiratory questionnaire for upper respiratory illness include throat

irritation, acute cough, cough with phlegm, wheeze, runny nose, breathing difficulty, fever, and earache.

Acute lower respiratory illnesses are generally classified into one of four clinical syndromes: croup (laryngotracheobronchitis), tracheobronchitis, bronchiolitis, and pneumonia (Glezen and Denny, 1973; Wright et al., 1989; McConnochie et al., 1988). In a study in Tucson, the most common diagnosis during the first year of life was bronchiolitis, which accounts for 60% of all lower respiratory illness (Wright et al., 1989). The most common signs and symptoms associated with lower respiratory illnesses were wet cough (85%), wheeze (77%), tachypnea (48%), fever (54%), and croupy cough (38%) as reported by Wright et al. (1989). A few infectious agents are presumed to cause the majority of childhood lower respiratory illness. Bacteria are not thought to be common causes of lower respiratory illness in nonhospitalized infants in the United States (Wright et al., 1989). Seventy-five percent of the isolated microbes were one of four types: RSV, parainfluenza virus types 1 and 3, and *Mycoplasma pneumoniae* (Glezen and Denny, 1973; McConnochie et al., 1988). Respiratory syncytial virus is particularly likely to cause lower respiratory illness during the first two years of life. More than half of all illnesses diagnosed as bronchiolitis, for which an agent was identified, were positive for RSV (Wright et al., 1989). Wright et al. (1989) noted that studies that rely on parental reports of symptoms may underestimate illness. Asking parents about illnesses at the end of the first year of life revealed that one-third of them failed to report illnesses diagnosed by pediatricians.

Various studies of lower respiratory illness have reported rates based on visits to physicians ranging from about 20 to 30 illnesses/100 children in the first year of life (Glezen and Denny, 1973; Wright et al., 1989; Denny and Clyde, 1986; McConnochie et al., 1988). Glezen and Denny (1973) reported that the rate for lower respiratory illnesses ranged from 24/100 person-years in infants under one year of age and decreased steadily each year through the preschool years, tending to level off in school children (age 12 to 14 years) to about 7.5 illnesses/100 person-years. Several factors affect the rate of lower respiratory illness in children, including age, immunologic status, prior viral infections, siblings of early school age, level of health, SES (Chanock et al., 1989), day care attendance, home dampness and humidity, environmental tobacco smoke, NO_2, PM, and other pollutants. Rates also depend on method of illness ascertainment. Studies in the United States (Wright et al., 1989; Denny and Clyde, 1986;

McConnochie et al., 1988) indicated that the overall pattern and incidence of lower respiratory illness is consistent in different geographic regions during the two decades covered by the studies, suggesting that diagnosis and infectious agents have changed little in that time period. Lower respiratory illness remains one of the major causes of childhood morbidity in the United States (McConnochie et al., 1988).

Over the past 4 decades, a large body of epidemiologic evidence has accumulated that indicates that respiratory illness events in childhood (mostly viral) are important determinants (risk factors) for the future risk of chronic respiratory symptoms and disease in adult life (Samet et al., 1983; Denny and Clyde, 1986; Britten et al., 1987; Glezen, 1989; Gold et al., 1989). Based on such data, it seems likely that any factor such as PM that could be responsible for increasing the risk of childhood respiratory illness and symptoms would be of considerable public health importance not only with regard to immediate morbidity, but also in relation to its contribution to chronic respiratory disease morbidity later in life.

Studies of Respiratory Illness in Children

Schwartz et al. (1994) analyzed respiratory symptoms in children from the Harvard Six Cities Studies. The cities included Watertown, MA; St. Louis, MO; Portage, WI; Kingston-Harriman, TN; Steubenville, OH; and Topeka, KS. Daily diaries of respiratory symptoms were collected from the parents of 1844 school children for one year starting in September, 1984. A centrally located residential monitor measured SO_2, NO_2, and O_3 on a continuous basis, $PM_{2.5}$ and PM_{10} were collected by a dichotomous sampler ,and aerosol acidity was measured daily. A multiple logistic regression model was used to analyze the data, adjusting for serial correlation by autoregressive terms estimated using the generalized estimating equations of Liang and Zeger (1986). The only weather variable included in the model was temperature, using both linear and quadratic terms.

In order to avoid the seasonal component of respiratory illness, the analysis was restricted to the months of April through August. During this period the $PM_{2.5}$ values had a median value of 18 $\mu g/m^3$ with 10th and 90th percentile values of 7.2 and 37.0 $\mu g/m^3$. The PM_{10} values had a median value of 30 $\mu g/m^3$ with 10th and 90th percentile values of 13 and 53 $\mu g/m^3$. Sulfate fractions were estimated from the $PM_{2.5}$ filters. The strongest relationships for cough were found with PM_{10} and O_3, and these effects appeared to be independent of each other. An

increase of 30 μg/m^3 in PM_{10} was associated with an odds ratio for cough of 1.28 (1.07 to 1.54). Fitting a non-parametric Generalized Additive Model showed that cough incidence increased monotonically with PM_{10} concentration, and there was no evidence of non-linearity. Lower respiratory symptoms (LRS) were also related to all pollutants except acidity. Strongest relationships were found with PM_{10} and sulfate fraction, and these effects appeared to be independent of each other. An increase of 30 μg/m^3 in PM_{10} was associated with an odds ratio for lower respiratory symptoms of 1.53 (1.20 to 1.95). There was no evidence of non-linearity, as shown in Figure 12-2. Comparable analyses for SO_2 and H^+ are shown in Figures 12-3 and 12-4. Note that these curves show an inconsistent relationship at lower exposure estimates. Although these non-parametric models do not provide confidence intervals, it is clear that the relationship between cough and PM_{10} is stronger than for either SO_2 or H^+.

Pope et al. (1991) studied respiratory symptoms in asthmatic school children in the Utah Valley. Participants were selected from samples of 4th and 5th grade elementary students in 3 schools in the immediate vicinity of PM_{10} monitors in Orem and Lindon, Utah and were restricted to those who responded positively to one of: (a) ever wheezed without a cold; (b) wheezed for 3 days out of a week for a month or longer; (c) had a doctor say the "child has asthma". This resulted in 34 subjects who were included in the final analyses. PM_{10} monitors operated by the Utah State Department of Health collected 24 h PM_{10} samples from midnight to midnight (range 11 to 195 μg/m^3) with an average of approximately 46 μg/m^3. There was limited monitoring of SO_2, NO_2, and O_3. Lower respiratory disease was defined as the presence of at least one of: trouble breathing, dry cough, or wheezing. A fixed effects logistic regression analysis was calculated using each person as his own control and low temperature as a covariate. Estimated odds ratios for upper respiratory disease per PM_{10} increase of 50 μg/m^3 was 1.20 (1.03, 1.39); for lower respiratory illness, it was 1.28 (1.06, 1.56).

Pope et al. (1991) also studied asthmatics aged 8 to 72 in the Utah Valley, selected from those referred by local physicians. This resulted in 21 subjects who were included in the final analysis. The same air quality data were used. Lower respiratory disease was

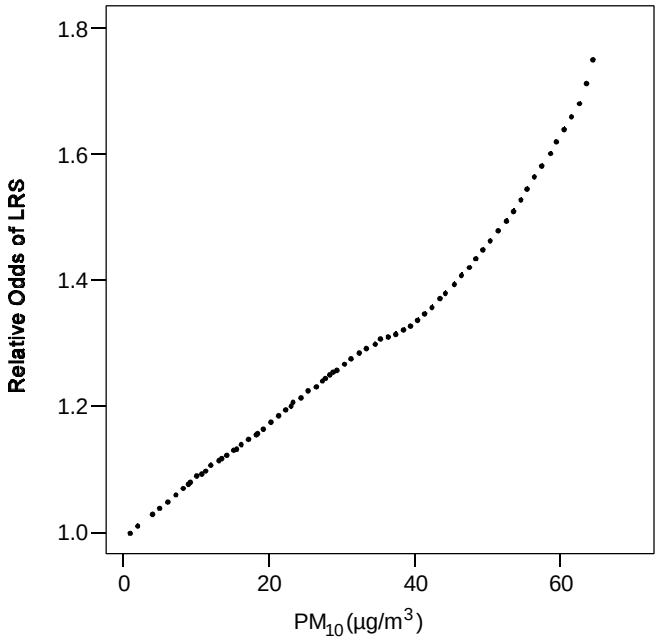

Figure 12-2. Relative odds of incidence of lower respiratory symptoms (LRS) smoothed against 24-h mean PM_{10} ($\mu g/m^3$) on the previous day, controlling for temperature, day of the week, and city.

Source: Schwartz et al. (1994).

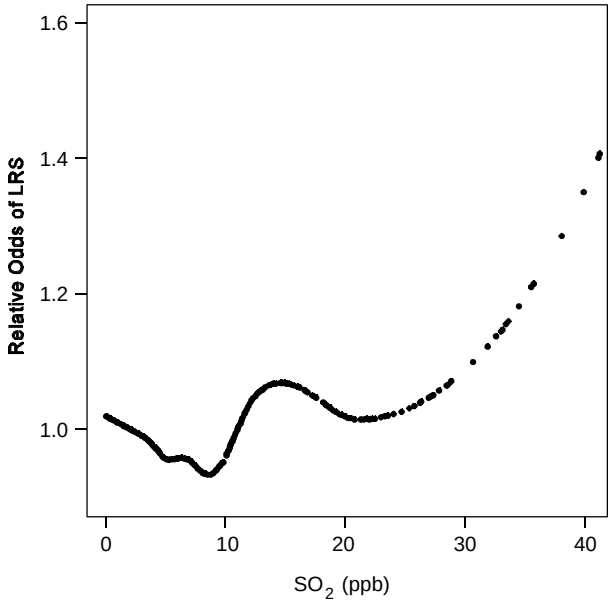

Figure 12-3. Relative odds of incidence of lower respiratory symptom (LRS) smoothed against 24-h mean sulfur dioxide (SO_2) concentration on the previous day, controlling for temperature, city, and day of the week.

Source: Schwartz et al. (1994)

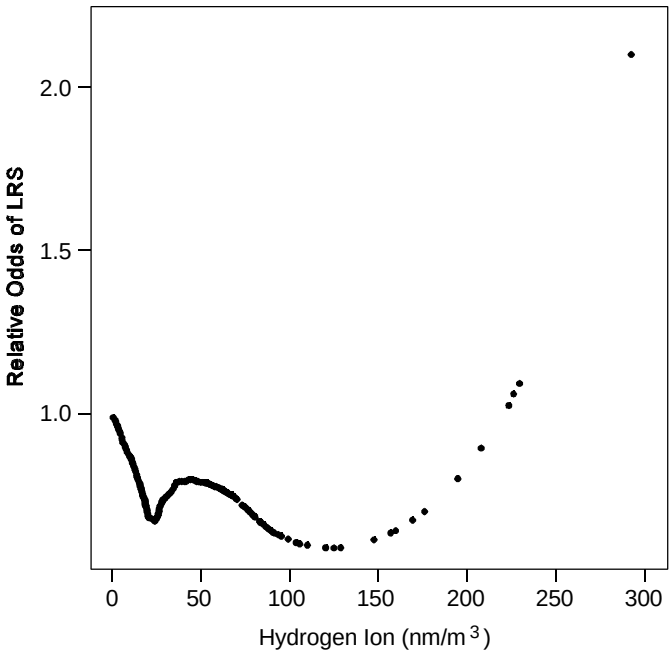

Figure 12-4. Relative odds of incidence of lower respiratory symptom smoothed against 24-h mean hydrogen ion concentration on the previous day, controlling for temperature, city, and day of the week.

Source: Schwartz et al. (1994)

defined the same for this group of subjects. A fixed effects logistic regression analysis was calculated using each person as his own control and low temperature as a covariate. The estimated odds ratio for upper respiratory disease per PM_{10} increase of 50 μg/m^3 in PM_{10} was 0.99 (0.81, 1.22). For lower respiratory illness, it was 1.01 (0.81, 1.27).

In a follow up study, Pope and Dockery (1992) enrolled non-asthmatic symptomatic and asymptomatic children in the Utah Valley, selected from samples of 4th and 5th grade elementary students in three schools in the immediate vicinity of PM_{10} monitors in Orem and Lindon Utah. A questionnaire identified 129 children who were mildly symptomatic and 60 were selected. An additional 60 with no symptoms were recruited. PM_{10} monitors operated by the Utah State Department of Health collected 24 h samples from midnight to midnight; PM_{10} values averaged 76 μg/m^3 during the study period and ranged from 7 to 251 μg/m^3. No SO_2 and limited NO_2 and O_3 monitoring were conducted. Low temperature was used to adjust for weather, but no adjustment was made for humidity. Upper respiratory symptoms had a logistic

regression coefficient of .00519 (.00203) and lower respiratory symptoms had a coefficient of .00658 (.00205) in the symptomatic sample using a 5-day moving average of PM_{10}. These correspond to odds ratios of 1.30 and 1.39 respectively for an increase of 50 $\mu g/m^3$ in PM_{10}. No consistent effects were seen in the asymptomatic sample, although all effects tended to increase with PM. Only minimum temperature was used to adjust for weather.

Ostro et al. (1995) studied a panel of 83 African-American asthmatic children aged 7 to 12 recruited from four allergy and pediatric clinics in central Los Angeles and two asthma camps in the summer of 1992. The analysis focused on the daily reporting of respiratory symptoms including shortness of breath, cough, and wheeze. Daily air monitoring at three fixed sites included O_3, PM_{10}, NO_2, and SO_2. PM_{10} levels ranged from 20 to 101 $\mu g/m^3$ and O_3 from 10 to 160 ppb. Daily temperature, humidity, rainfall, pollens and molds were also used as covariates. A logistic regression allowing for repeated measures with variances estimated by generalized estimating equations was used to estimate effects of the pollutants and covariates. Both PM_{10} and O_3 were associated with increased shortness of breath, and the authors could not separate the effect of the two pollutants. The odds ratio for an increase of 56 $\mu g/m^3$ PM_{10} was 1.58 (1.05, 2.38). No effects were seen with cough or wheeze.

Schwartz et al. (1991a) analyzed acute respiratory illness in children in five German communities. Children's hospitals, pediatric departments and pediatricians were asked to fill out a short questionnaire for each visit for croup or obstructive bronchitis over a 2-year period. A diagnosis of croup was defined as acute stenotic subglottic laryngotracheitis. Not all doctors reported for the full 2 years—a loss of about 50%. Thus, participation was about 50%. Areas chosen to represent a wide range of air pollution exposure included: Duisburg and Köln in the highly industrialized areas of Northrhine-Westfalia and Stuttgart, and Tubingen/Reutlingen and Freudenstadt in South Germany. One to four TSP monitors were located in each study areas and 24 h measurements were taken of TSP, SO_2, and NO_2. TSP was measured by low volume sampler, NO_2 by chemiluminescence, and SO_2 by the conductometric method, and were expressed in $\mu g/m^3$. Poisson regression analysis as described by McCullagh and Nelder (1983) was used to estimate the effect of pollution on croup and obstructive bronchitis, with adjustments for serial correlation using the method of Zeger and Liang (1986). The model included terms for season (annual and biannual sine and cosine terms), weather (temperature and relative humidity), and drop-outs. Logistic regression coefficients estimated from the Poisson

regressions gave values of 0.1244 admissions/log(TSP) (.0309), 0.4161 (.156) for NO_2, and 0.0831 (.0352) for SO_2. The log TSP coefficient was not significant when either NO_2 or SO_2 were included in the model.

Hoek and Brunekreef (1993) and Hoek (1992) studied a general population sample of 112 children aged 7 to 12 who lived in the nonindustrial town, Wageningen, NL. Acute respiratory symptoms of the children were recorded in a diary by their parents, including throat irritation, cough, cough with phlegm, wheeze, runny nose, and a variety of other symptoms. PM_{10} was measured daily (3PM to 3PM) with an inlet design similar to the Sierra Anderson 241 dichotomous sampler. SO_2 was measured using fluorescence, and NO_2 was measured using chemiluminescence. Logistic regression analyses including first order autoregressive terms were used to analyze the data and included ambient temperature and day of study as covariates. The PM_{10} coefficient for any upper respiratory illness was 0.0026 (0.0013). This corresponds to an odds ratio of 1.14 (95% confidence interval of (1.00 to 1.30) for an increase of 50 $\mu g/m^3$ PM_{10}. Most other coefficients were not significant.

Braun-Fahrländer et al. (1992) studied daily respiratory disease symptoms in preschool children in 4 areas of Switzerland. A sample of 840 children was chosen from Basel and Zurich. One-twelfth of the sample was recruited each month from November 1985 to November 1986. A physician conducted a standardized questionnaire with the parents. Parents recorded daily symptoms including cough without runny nose, breathing difficulty, and fever with earache and sore throat. TSP was measured daily (method not given) and NO_2 by Palmes tubes both outside the apartment and inside the room where the child stayed most frequently. Children lived within 6 km of an outdoor monitor which measured TSP, NO_2, SO_2, and O_3. Multiple logistic regression analysis was used to explain differences in upper respiratory symptom incidence. Analysis terms included temperature, season, city, and a risk strata based on a cross-sectional analysis. Variances were adjusted using the method of Liang and Zeger (1986). The TSP coefficient for upper respiratory symptoms was 0.00454 (0.00174), corresponding to an odds ratio of 1.57 per TSP increase of 100 $\mu g/m^3$. Neither NO_2, SO_2, or O_3 were significant.

Hoek and Brunekreef (1994) studied pulmonary function and respiratory symptoms in more than 1000 children in 4 towns in the Netherlands. Children aged 7 to 11 in Deurne, Enkhuizen, Venlo, and Nijmegen were studied during one of three winters (1987/88, 1988/89, 1989/90). During the study, respiratory symptoms data were collected daily by diary. PM_{10} was

measured daily (3PM to 3PM) with an instrument inlet design similar to the Sierra Anderson 241 dichotomous sampler, SO_2 by fluorescence, and NO_2 by chemiluminescence. Separate logistic regressions were performed for 9 locations (six groups of subjects of Deurne and one in each other town) using a first order autoregressive model. The coefficients were combined using the inverse variance weighting method. The odds ratio for the incidence of cough associated with 100 $\mu g/m^3$ PM_{10} increase was 1.10 (0.67,1.79). PM_{10} odds ratios for upper and lower respiratory illness were also not statistically significant. Nor was the incidence of acute respiratory symptoms significantly related to PM_{10}, SO_2, NO_2, or sulfate.

In a winter study by Roemer et al. (1993) of children with chronic respiratory symptoms, parents of children in grades 3 to 8 in two small nonindustrial towns in the Netherlands were given questionnaires about respiratory symptoms. Seventy-four of the 131 children with positive responses (cough or shortness of breath) were included in the study. PM_{10} was measured daily using an instrument inlet design similar to the Sierra Anderson 241 dichotomous sampler. SO_2, NO_2, and black smoke were also measured. Several symptoms including asthma attack, wheeze, and cough were marginally associated with PM_{10}. The logistic regression coefficient for wheeze was .00224 (.00115) per unit increase in the same day's PM_{10} level. The coefficient for broncho-dilator use was .00210 (.00085). SO_2 and black smoke were also marginally related to several of the symptoms.

Hoek and Brunekreef (1995) studied respiratory symptoms in 300 children aged 7 to 11 years in Duerne and Enkhuizen, The Netherlands. The study was designed as an ozone study, but SO_2, NO_2, and PM_{10} were also measured (PM_{10} ranged 13 to 124 $\mu g/m^3$; O_3 ranged 22 to 107 ppb). A symptom diary similar to that used in the Harvard Six Cities Study was used to obtain daily information on cough, phlegm, wheeze, runny nose, and other respiratory symptoms. A multiple logistic model with first order autoregressive residuals was used. Additional analyses using ARIMA models to allow for autocorrelation confirmed results of the logistic analyses. Nearly all logistic regression coefficients were non-significant and negative. The analyses of cough in Deurne gave an estimated odds ratio of 0.93 for a 50 $\mu g/m^3$ increase in PM_{10} on the same day. Analyses of other endpoints, lag times, and pollutants gave similar results.

Relationships between air pollution indices for 84 standard metropolitan statistical areas (SMSA`s) mostly of 100,000 to 600,000 people in size and indices of acute morbidity effects were studied by Ostro (1983), Hausman et al. (1984), and Ostro (1987), using data derived from

the National Center for Health Statistics (NCHS) Health Interview Survey (HIS) of 50,000 households comprising about 120,000 people. Ostro (1983) used HIS data to assess the prevalence of illness and illness-related restrictions in activity in the United States. Data on either restricted activity days (RADs) or work loss days (WLDs) were aggregated over a year, and correlated with annual TSP levels, controlling for temperature, wind, precipitation, population density, and smoking. Using the 1976 survey, a significant relationship between TSP and both outcomes was found, with RAD's being more significant. Sulfate fractions were not significantly related to either outcome. Ozone was not measured. The explained variation was much higher for RADs than for WLDs. The average of air pollution monitors for each city was used, rather than aerometric data aggregated for smaller geographic units in relationship to individuals residing nearby for whom HIS data were included in the analysis. Hausman et al. (1984) analyzed the same data, but used Poisson regression analysis using a fixed effects model that compared deviations from the city mean levels of illness and short-term pollution as the exposure variable. Significant associations between 2-week average TSP levels and RADs or WLDs were found. The magnitude of the within city effects was similar to the magnitude of the between city effects seen earlier. Demographic factors were controlled for on an individual basis, along with climatic conditions.

Ostro (1987) applied the Hausman et al. (1984) techniques to analyze HIS results from 1976 to 1981 in relation to estimates of fine particle (FP) mass. That is, for adults aged 18 to 65, days of work loss (WLDs), restricted activity days (RADs) and respiratory-related restricted activity days (RRADs) measured for a 2-week period before the day of the survey were used as measures of morbidity and analyzed in relation to estimated concurrent 2-week averages of FP or lagged in relation to estimated 2-week FP averages from two to four weeks earlier. The FP estimates were produced from the empirically derived regression equations of Trijonis. These equations incorporated screened airport data and 2-week average TSP readings at population-oriented monitors, using data taken from the metropolitan area of residence. Various potentially confounding factors (such as age, race, education, income, existence of a chronic health condition, and average 2-week minimum temperature) were controlled for in the analyses. The morbidity measures (WLDs, RADs, RRADs), for workers only or for all adults in general, were consistently found to be significantly ($p < 0.01$ or < 0.05) related to lagged FP estimates (for air quality 2 to 4 weeks prior to the health interview data period), when analyzed for each of the

individual years from 1976 to 1981. However, less consistent associations were found between the health endpoints and more concurrent FP estimates.

Ostro and Rothschild (1989) studied acute respiratory morbidity based on an analysis of 1976 to 1981 HIS data. Ozone measurements were taken from EPA's SAROAD monitoring network, and FP measurements were estimated from airport visibility data. The endpoints of the analysis included minor restrictions in activity and work loss. Using a multiple regression analysis, both endpoints showed a relationship to FP.

School Absences Studies

Most school absences are due to acute conditions (Klerman, 1988). Respiratory conditions are the most frequent cause, particularly influenza and the common childhood infectious diseases. School absences are also caused by injuries, digestive system conditions and ear infections. Kornguth (1990) notes the following characteristic of school absent children: (1) as mothers level of education or family income increased the likelihood of their children being absent decreased; and (2) days absent due to illness are related to source of medical care and to type of health insurance coverage. Children with a wide range of chronic illnesses miss more school than their healthy peers. There is only tentative evidence that school absent rates of individual children vary directly with the severity of their health problem (Weitzman, 1986). Parcel et al. (1979) found that children with asthma have a significantly higher absentee rate than do nonasthmatic children. Children who smoke and whose parents smoke are more likely to be absent from school for minor ailments (Charlton and Blair, 1989). Whether this increased likelihood of absence is due to genuine health problems, or to a generally negative attitude to school in children who take up smoking to boost their self-esteem, is unclear.

Most excessive school absence is probably the result of factors outside the health care sphere (Klerman, 1988). Chaotic family environments, lack of achievement motivation, understaffed and uninviting schools, and other societal problems, are undoubtedly the major reason for absenteeism. Excessive school absence is a profound educational and social problem in the United States (Weitzman et al., 1986). Despite the fact that the majority of school absences are reported as being health related, data suggest that demographic and educational characteristics of students have a much greater influence on absence behavior than do health-related factors. Since school absence rates reflect both health and non-health related factors, it is

important that investigators recognize the nonspecific nature of the measure and account for non-health related influences appropriately (Weitzman, 1986). Such non-health related potential problems with the data include the following: data are difficult to collect, individual data as compared to aggregate data; different coding in schools for tardy or leaves school early for sickness; and, records may not be computerized at school, making retrospective studies more difficult (Weitzman, 1986).

Ransom and Pope (1992) studied elementary school absences in connection with the steel strike in the Utah Valley. Data for school absences from 1985 to 1991 were obtained from two sources: (1) district-wide attendance averages by grade level from the Provo School District, and (2) daily absenteeism records from the Northridge Elementary School in Orem. The Northridge School was much closer to the steel mill than were the schools in the Provo School District. Daily PM_{10} measurements were made at three sites (Linden, Provo, and Orem), but only the Linden site collected daily measurements for the entire time period of the study. Some SO_2 and O_3 measurements were available, but these values tended to be well below the National Ambient Air Quality standards. Meteorological information was available from the Brigham Young University weather station. Regression analyses were conducted, taking into account several covariates including month of study, snowfall, Christmas and Thanksgiving holidays, and low temperature. The best PM_{10} predictor was a 4-week moving average. A highly significant increase of about 2% in the absence rates (absolute increase) for an increase of 100 $\mu g/m^3$ increase in the 4-week average PM_{10} was found for both sets of data, and the coefficient was similar even when a dummy variable was added for the strike. No adjustments were made for periods of increased influenza cases.

Studies of Respiratory Illness in Adults

Lawther et al. (1970) reported on studies carried out from 1954 to 1968 mainly in London, using a diary technique for self-assessment of day-to-day changes in symptoms among bronchitic patients. A daily illness score was calculated from the diary data and related to BS and SO_2 levels and weather variables. Pollution data for most of the London studies were mean values from the group of sites used in the mortality/morbidity studies of Martin (1964). In early years of the studies, when pollution levels were generally high, well defined peaks in illness score were seen when concentrations of either BS or SO_2 exceeded 1,000 $\mu g/m^3$. With later

reductions in pollution, the changes in condition became less frequent and of smaller size. From the series of studies as a whole, up to 1968, it was concluded that the minimum pollution levels associated with significant changes in the condition of patients was a 24-h mean BS level of ~250 $\mu g/m^3$ together with a 24-h mean SO_2 concentration of ~500 $\mu g/m^3$ (0.18 ppm). A later study reported by Waller (1971) showed that, with much reduced average levels of pollution, there was an almost complete disappearance of days with smoke levels exceeding 250 $\mu g/m^3$ and SO_2 levels over 500 $\mu g/m^3$ (0.18 ppm). As earlier, some correlation remained between changes in the conditions of the patients and daily concentrations of smoke and SO_2, but the changes were small at these levels and it was difficult to discriminate between pollution effects and those of adverse weather. The analysis of the Lawther et al. (1970) study was made prior to the availability of current statistical methods such as poisson regression using generalized estimating equations. The large differences seen by Lawther et al. (1970) at high levels would undoubtedly remain significant regardless of the analysis technique.

Dusseldorp et al. (1994) studied respiratory symptoms in 32 adults living near a large steel plant in Wijk aan Zee, The Netherlands. During the study period PM_{10} levels ranged from 36 to 137 $\mu g/m^3$. Diary information on acute respiratory symptoms, medication use, and presence of fever was collected. Peak flow measurements were also taken. The study was conducted from 11 October 1993 to 22 December 1993, and the average number of days per subject was 66. A logistic regression model was used and to control autocorrelation, a linear time series model was also fitted. Both models gave similar results and so the logistic regression coefficients converted to odds ratios for 100 $\mu g/m^3$ were reported. These were converted to odds ratios for 50 $\mu g/m^3$. The odds ratio for cough on PM_{10} (lag zero) was 1.31 (0.9, 1.76). The other endpoints of phlegm, shortness of breath and wheeze showed lesser effects. Using PM_{10} lagged one, two, and three days showed little effect.

Lebowitz et al. (1982) studied 117 families in Tucson, AZ selected from a stratified sample of families in geographical clusters from a representative community population included in an ongoing epidemiologic study. Both asthmatic and non-asthmatic families were evaluated over a 2-year period using daily diaries. The health data obtained were related to various indices of environmental factors derived from simultaneous micro-indoor and outdoor monitoring in a representative sample of houses for air pollutants, pollen, fungi, algae and climate. Monitoring of air pollutants and pollen was carried out simultaneously. Two-month averages of indoor TSP

ranged from 2.1 to 169.6 $\mu g/m^3$. Cyclone measurements of respirable particulate (RSP) ranged from below minimum detectable limits up to 28.8 $\mu g/m^3$; CO and NO_2 measurements were also taken, but no $S0_2$ monitoring was reported. This appears to be one of the few studies monitoring indoor air. TSP and pollen were reported to be related to symptoms in both asthmatics and non-asthmatics, but the authors reported that the statistical analyses used were all qualitative (because of low sample size) and statistical significance was not computed.

Whittemore and Korn (1980) studied asthmatics in seven communities in the Los Angeles area. Panelists were located by consulting local physicians and were followed for 34 weeks from May 7 to December 30 in the years 1972 to 1974 from the communities of Santa Monica, Anaheim, Glendora, Thousand Oaks, Garden Grove, and Covina. Dairies were filled out weekly by the participants who gave daily information on symptoms. Monitoring stations were placed in each community near an elementary school. TSP, RSP, suspended sulfates, suspended nitrates, SO_2, and photochemical oxidants were measured. NO_2 was also measured but the data were determined to be unreliable. Because of the colinearities and measurement errors, only TSP and photochemical oxidants were actually included in the analyses. A logistic model was used for each individual that included the presence of an attack on the previous day, meteorology, day of study, day of week, and pollutants. Regression coefficients were combined using both a fixed and random effects model. Both photochemical oxidants and TSP were found to be significantly related to symptoms, even when the other pollutant was included in the model. The coefficient for TSP for both models was .00079 (standard error not given). This corresponds to an odds ratio of 1.08 for a 100 $\mu g/m^3$ increase in TSP.

Ostro et al. (1991) studied adult asthmatics recruited from clinic patients in Denver. Diagnosis of asthma was based on physical exam confirmed by lung function tests. The panel of 207 recorded daily symptoms and medication use from November 1987 to February 1988. Ambient air pollutants measured were sulfates, nitrates, $PM_{2.5}$, nitric acid, H^+, and SO_2 at a downtown Denver monitor two miles from the clinic. Logistic regression analysis was used with adjustment for autocorrelation by creating an instrumental variable; the final regression used Proc Autoreg in SAS. The coefficient for log($PM_{2.5}$) was .0006 (.0053) for asthma and .0012 (.0043) for cough. H^+ was the only pollutant near statistical significance, having an estimate coefficient of .0031 (.0042) for asthma and .0076 (.0038) for cough. The coefficients

cannot be compared directly with other studies because of the log transformation, and attempts to convert them based on mean values give unreasonable answers.

Ostro et al. (1993) studied respiratory symptoms in non-smoking adults aged 18 or more in Southern California from September 1978 to March 1979. The analysis was restricted to those 321 subjects who completed diaries for the entire 181-day period. The health endpoints included upper respiratory illness, lower respiratory illness, and eye irritation. Air pollution data for the Glendora, Covina, and Azusa areas were obtained from the Los Angeles County Air Pollution Control District Station in Azusa and included O_3, NO_2, SO_2, and sulfate fraction of PM. Temperature, rain, and humidity were used as meteorological covariates. A multiple logistic regression analysis was run using the three health endpoints. Ozone, sulfate fraction, and gas stove use were associated with significant odds ratios for lower respiratory tract illness. The odds ratio for gas stove use, 1.23, was well within the range reported in a meta-analysis of studies of nitrogen oxides by Hasselblad et al. (1992), but COH was not significantly related to lower respiratory illness. Only ozone was related to upper respiratory illness or eye irritation. The author did not report that adjustments were made for serial correlation of the health outcomes.

Acute Respiratory Illness Studies Summary

This category includes several different endpoints, but most investigators reported results for at least two of: (1) upper respiratory illness, (2) lower respiratory illness, or (3) cough (See Table 12-12 and Figure 12-5). The following relative risks are all estimated for an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The studies of upper respiratory illness do not show a consistent relationship with PM. Two of the studies showed no effect, three studies estimated an odds ratio near 1.2, and the study of Braun-Fahrländer et al. (1992) estimated the odds ratio of 1.55. Some of inconsistency could be explained by the fact that the studies included very different populations.

The studies of lower respiratory disease gave odds ratios which ranged from 1.10 to 1.28 except for the Schwartz et al. (1994) Six-Cities study, which gave a value over 2.0. Although the lower respiratory disease studies also include a variety of populations, it is difficult to explain the large range of estimates.

The studies of cough were more consistent, having odds ratios ranging from 0.98 to 1.51. Again, the Schwartz et al. (1994) study produced the largest value. The second highest value was that of 1.29 from Pope and Dockery (1992).

All three endpoints had the same general pattern of results. Nearly all odds ratios were positive, and about half were statistically larger than 1. Each endpoint had one study with a very high odds ratio. This can be compared with the hospital admission studies which all resulted in very similar estimates. There are several factors which could account for this. The respiratory disease studies used a wide variety of designs. As a result, the models for analysis were also varied. Finally, the populations included several different subgroups whereas the hospitalization studies tended to include similar populations.

There were fewer studies of respiratory symptoms in adults as compared with those in children. Whittemore and Korn (1980) found a relationship between TSP and asthma attacks in a panel of asthmatics. The estimated effect corresponded to an odds ratio of 1.08 for a 100 $\mu g/m^3$ increase in TSP. However, Ostro et al. (1991) found no relation between asthma or cough with $PM_{2.5}$ in asthmatics in Denver. No other studies estimated quantitative relationships.

12.3.2.3 Pulmonary Function Studies

Pulmonary function studies are part of any comprehensive investigation of possible effects of an air pollutant. Measurements can be made in the field, they are noninvasive, and the reproducability of some lung function measures has been well documented. Also,

TABLE 12-12. ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range[1]	Ave. Rate per Day	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Other Pollutants in Model	Result[2] (Confidence Interval)
Schwartz et al. (1994), study of respiratory symptoms in 6 U.S. cities, 1984-1988	Daily data for PM_{10}, $PM_{2.5}$ at each city	median PM_{10} 30 µg/m^3; 10% tile 13, 90% tile 53. median $PM_{2.5}$ 18 µg/m^3; 10% tile 7, 90% tile 37.	(not given)	Autoregressive logistic regression using GEE	SO_2, median 4 ppb; 10% tile 1 ppb, 90% tile, 18 ppb. NO_2, median 13 ppb; 10% tile 5 ppb; 90% tile 24 ppb O_3.	Temp., day of week, city or residence	All two pollutant models fitted with minimal effect on PM	Cough (PM_{10} lag 1): 1.51 (1.12, 2.05) Upper resp. (PM_{10} lag 2): 1.39 (0.97, 2.01) Lower resp. (PM_{10} lag 1): 2.03 (1.36, 3.04)
Pope et al. (1991), study of students in Utah Valley, winter 1989-1990	PM_{10} data for stations at 3 sites	mean 46 µg/m^3; range 11 to 195 μg/m^3	(not given)	Fixed effects logistic regression	Limited monitoring of NO_2, SO_2, and O_3. Values well below NAAQS.	Variables for temp. and time trend	none	Upper resp. 1.20 (1.03, 1.39) Lower resp. 1.28 (1.06, 1.56)
Pope et al. (1991), study of asthmatic children in Utah Valley, winter 1989-1990	PM_{10} data for stations at 3 sites	mean 46 µg/m^3; range 11 to 195 μg/m^3	(not given)	Fixed effects logistic regression	Limited monitoring of NO_2, SO_2, O_3. Values well below NAAQS.	Variables for low temp. and time trend	none	Upper resp. 0.99 (0.81, 1.22) Lower resp. 1.01 (0.81, 1.27)
Pope and Dockery (1992), symptomatic children in the Utah Valley, winter 1990-1991	PM_{10} data for stations at 2 sites	mean 76 µg/m^3; range 7 to 251	(not given)	Autoregressive logistic regression using GEE	none	Variable for low temp.	none	Upper resp. 1.20 (1.03, 1.39) Lower resp. 1.27 (1.08, 1.49) Cough 1.29 (1.12, 1.48)

TABLE 12-12 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range[1]	Ave. Rate per Day	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Other Pollutants in Model	Result[1] (Confidence Interval)
Pope and Dockery (1992), asymptomatic children in the Utah Valley, winter 1990-1991	PM_{10} data for stations at 2 sites	mean 76 µg/m^3; range 7 to 251	(not given)	Autoregressive logistic regression using GEE	none	Variable for low temp.	none	Upper resp. 0.99 (0.78, 1.26) Lower resp. 1.13 (0.91, 1.39) Cough 1.18 (1.00, 1.40)
Hoek and Brunekreef (1993), respiratory disease in school children aged 7 to 12 in Wageningen, NL, winter 1990-1991	PM_{10} data for 2 to 4 stations	max 110 µg/m^3	(not given)	Autoregressive logistic regression using GEE	Max SO_2 105 µg/m^3; max NO_2 127 µg/m^3	Variable for ambient temp. and day of study	none	Upper resp. 1.14 (1.00, 1.29) Lower resp. 1.06 (0.86, 1.32) Cough 0.98 (0.86, 1.11)
Schwartz et al. (1991a), study of acute respiratory illness in children in five German communities, 1983-1985	Two to 4 monitoring stations in each area measured TSP	medians 17 to 56 µg/m^3; 10% tiles 5 to 34; 90% tiles 41 to 118	0.5 to 2.9	Autoregressive Poisson regression using GEE	median SO_2 levels ranged 9 to 48 µg/m^3, median NO_2 levels ranged 14 to 5 µg/m^3	Most stat. significant terms of day of week, time trend, and weather	none (TSP not stat. significant when NO_2 added to model)	1.26 (1.12, 1.42)
Braun-Fahrländer et al. (1992), study of preschool children in four areas of Switzerland	Daily data for TSP	(not given)	4.4	Logistic regression	SO_2, NO_2, and O_3 levels not given	City, risk strata, season, temperature	none	Upper resp. 1.55 (1.10, 2.24)
Roemer et al. (1993), study of children with chronic resp. symptoms in Wageningen, NL.	Daily data PM_{10}	6 days above 110 µg/m^3	.094 incidence rate	Autoregressive logistic regression	SO_2 and NO_2 means not given	(not given)	none	Cough (not given, probably less than one)

TABLE 12-12 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range[1]	Ave. Rate per Day	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Other Pollutants in Model	Result[2] (Confidence Interval)
Dusseldorp et al. (1994) Study of adults near a Netherlands steel mill	Daily data for PM_{10}, iron, sodium, silicon, and manganese	mean PM_{10} 54 µg/m^3; range 4 to 137	(not given)	Logistic regression	Geometric mean iron 501 ng/m^3; manganese 17 ng/m^3; silicon 208 ng/m^3	(not given)	none	Cough 1.14 (0.98, 1.33)
Ostro et al. (1991), study of adult asthmatics in Denver, Colorado November 1987 to February 1988	Two monitors provided daily measurements of $PM_{2.5}$	22 µg/m^3; range 0.5 to 73 μg/m^3	15 (out of 108)	Autoregressive logistic regression	nitric acid, sulfates, nitrates, SO_2, and hydrogen ion	Day of week, gas stove, min. temp.	none	Cough 1.09 (0.57, 2.10)
Ostro et al. (1993), study of non-smoking adults in Southern California	Apparently one site (Azusa). PM measurements included sulfate and COHS	mean sulfate 8 µg/m^3; range 2 to 37 μg/m^3 mean COHS 12 per 100 ft; range 4 to 26	4.2/person for lower resp., 10.2/person, upper resp.	Logistic regression	ozone, mean = 7 pphm, range = 1 to 28	Temp., none rain humidity	none	Sulfates: Upper resp. 0.91 (0.73, 1.15) Lower resp. 1.48 (1.14, 1.91)
Ostro et al. (1995), study of 83 African-American asthmatic children in Los Angeles	3 sites measured PM_{10}, O_3, NO_2, SO_2	PM_{10} ranged 20 to 101 μg/m^3 mean 56 μg/m^3	Not given	Logistic regression using GEE method	O_3, NO_2, SO_2	Humidity, temp., pollens, molds	O_3	Shortness of breath increase per a 56 μg/m^3 PM_{10} increase was 1.58 (1.05, 2.3). No effect on cough or wheeze.

TABLE 12-12 (cont'd). ACUTE RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range[1]	Ave. Rate per Day	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Other Pollutants in Model	Result[2] (Confidence Interval)
Hoek and Brunekreef (1995), study of respiratory symptoms in 300 children in 2 Netherlands communities	2 sites measured PM_{10}, O_3, sulfate, nitrate	Deane PM_{10} mean 48 $\mu g/m^3$ (range 13-124); Enkhulzen PM_{10} a mean 36 $\mu g/m^3$ (range 11-136)	Cough 5.5, LRS 1.5	Time series analyses (Box-Jenkins approach logistic regression model)	O_3, sulfate, nitrate	Trend, day of week, humidity		Logistic regression coefficient was -.0014 (-.0032, .0004) for PM_{10}. Similar coefficients for LRS, and any respiratory symp.

[1]Both mean and/or range provided as reported in cited paper.
[2]Odds ratio calculated from parameters given in published paper, assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

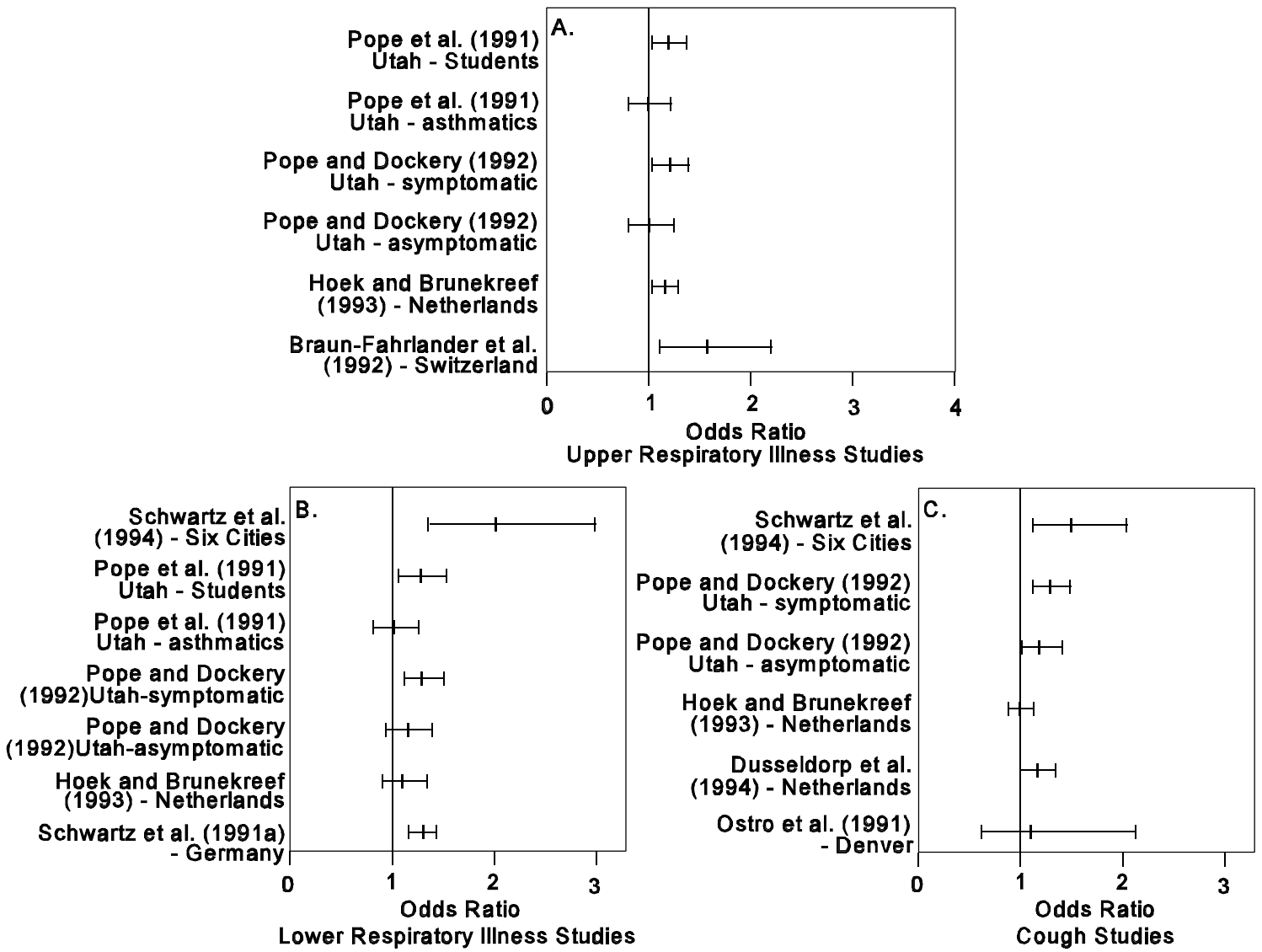

Figure 12-5. Odds ratios for acute respiratory disease (upper respiratory illness, lower respiratory illness, and cough) for a 50 $\mu g/m^3$ increase in PM_{10} (or equivalent) for selected studies.

guidelines for standardized testing procedures reference values, and interpretative strategies exist for lung function tests (American Thoracic Society, 1987, 1991).

Various factors are important determinants of lung function measures. For example, lung function in childhood is primarily related to general stature (as measured by height and, for children, by age). The growth patterns differ between males and females. Compared to girls, boys show larger size-adjusted (usually height or height^2) average values for various measures of lung function (Wang et al., 1993a,b). Moreover, growth of measures derived from forced expiratory maneuvers (e.g., forced vital capacity-FVC and forced expiratory volume one-second-FEV_1) continues for a longer period of time in males, beyond the time when height growth is complete (Wang et al., 1993a,b). Lung function begins to decline with age in the 3rd to 4th decades (Tager et al., 1988) and continues to do so monotonically as people age. Cigarette smoking, the presence of chronic obstructive lung disease, and/or asthma are some factors related to more rapid declines in lung function in adults (Tager et al., 1988; Vedal et al., 1984).

Factors in the environment undoubtedly influence the natural history of the growth and decline of lung function. Several such factors (viral respiratory illness, active smoking and passive exposure to tobacco smoke products) are briefly discussed here.

As in older children and adults, clinically inapparent alterations in lower airway function can occur during upper respiratory infections (URI) in infants (Martinez et al., 1990). Both differences in the caliber or length of the airway and differences in the elasticity of the lungs and chest wall may exist between infants who subsequently have wheezing with a viral lower respiratory tract illness and those who do not have wheezing with a similar illness. Thus the initial airway caliber, length, or both (and perhaps the structure of the lung parenchyma) may predispose infants to wheezing in association with common viral respiratory infection (Martinez et al., 1988; Tager et al., 1993; Martinez et al., 1991; Martinez et al., 1995).

Active smoking is the major risk factor for chronic airflow limitation. As a group, cigarette smokers have more rapid reductions in lung function with age relative to non-smokers. In approximately 15 to 20% of long-term regular smokers, this increased loss of lung function leads to the development of symptomatic chronic obstructive lung disease. Smoking cessation can be associated with recovery of a very small amount of function and a lessening of the rate of

decline of function (Dockery et al., 1983). However, such cessation amongst persons with far advanced chronic obstructive lung disease has little effect on the overall course of the disease.

Passive exposure to products of tobacco smoke generated by parental smoking has consistently been associated with alterations in lung function in infants and children. Maternal smoking, in particular, has demonstrated an exposure-response association with reduced lung function. The extensive body of evidence demonstrating this association has been reviewed by the U.S. Environmental Protection Agency (1992). The issue of passive exposure to tobacco smoke has particular conceptual relevance to the issue of the health effect of ambient PM, since tobacco smoke is a major PM source in indoor environments.

Studies of Pulmonary Function in Children

Dockery et al. (1982) studied changes in lung function in school age children as the result of air pollution episodes in Steubenville, OH — one of the cities in Harvard Six-City Study. Steubenville was known to have large changes in SO_2 and TSP exposures, such occurred in fall, 1978; fall, 1979; spring, 1980; and fall, 1980. During each period, lung function measurements ($FEV_{0.75}$ and FVC) were taken prior to the episode and within a week after the episode. Linear regression was used to estimate the effect of pollution on each child separately. The slopes were summarized by time period and combined into a total summary. The pooled slopes were significantly different from zero for for both $FEV_{0.75}$ and FVC in relation to both TSP and SO_2. The median slope for $FEV_{0.75}$ with TSP was −0.018 ml per $\mu g/m^3$ and for FVC it was −0.081 ml per $\mu g/m^3$.

Brunekreef et al. (1991) further analyzed data from Dockery et al. (1982) on pulmonary function in children in Steubenville, OH as part of the Harvard Six-Cities Study. Linear decreases in forced vital capacity (FVC) with increasing TSP concentrations were found, and slopes were determined for linear relationships fitting the data for four different observation periods (fall, 1978; fall, 1979; spring, 1980; fall, 1980). The slope of FVC versus TSP was calculated for 335 children with three or more observations during any of the four study periods, with 194 having been tested during more than one study period. Individual regression coefficients for each child using pollution as the independent variable were calculated. The distribution of coefficients was then trimmed to eliminate outliers. Slopes for TSP using one

and five day averages were significantly lower than zero for both FVC and $FEV_{0.75}$. No overall dose-response relationship was estimated.

During November, 1984, Dassen et al. (1986) obtained baseline pulmonary function data for approximately 600 Dutch children aged 6 to 11. Then, a subset of the same children (N = 62) was retested in January, 1985, during an air pollution episode when 24-h mean values for TSP (hi-vol samples), RSP (respirable suspended particulate, cyclone sampler), and $S0_2$ (acidimetric technique) measured via a 6-station network all reached 200 to 250 $\mu g/m^3$. Lung function values of 62 children were taken at the end of the episode. Growth adjusted FVC values decreased by an average of 62 ml (11), $FEV_{1.0}$ values by 50 ml (10), and Peak Expiratory Flow Rate (PEFR) values by 219 ml/sec (62), all statistically significant decreases. Several lung function parameters showed statistically significant average declines of 3 to 5% at second (episode) testing compared to each child's own earlier baseline values, including decrements in both FVC and FEV levels on the second day of the episode, as well as for measures reflecting small airway functioning (i.e., maximum mid-expiratory flow and maximum flow at 50% vital capacity). Declines from their original baseline values for these parameters were still seen 16 days after the episode upon retesting of another subset of the children, but no differences were found between baseline and retest values for a third subset of children reevaluated 25 days after the episode. The 24-h mean TSP, RSP, and SO_2 levels measured in the 100 to 150 $\mu g/m^3$ range just prior to the last lung function tests may not have been sufficient to cause observable pulmonary function effects in children.

Quackenboss et al. (1991) reported results of a lung function study of asthmatic children aged 6 to 15 years in Tuscon, AZ. The data were collected over two week periods from May 1986 to November 1988. Peak flow rates (PEFR) were measured with mini-Wright peak flow meters with three tests during each of four time periods per day (morning, noon, evening, bed). Activity patterns were recorded in diaries, as well as symptoms and medication use. Measurements of $PM_{2.5}$, PM_{10}, and NO_2 were made both inside and outside the home during the two week period for 50% of the homes. $PM_{2.5}$ levels were elevated in homes with environmental tobacco smoke. Exposures for the remaining homes were estimated statistically. A random effects linear model was used to estimate the effect of pollutants and other covariates on PEFR. The NO_2 levels had the greatest effect on PEFR rates, but the indoor $PM_{2.5}$ levels were associated with a 15 ml/s decrease in morning PEFR (within day change) per unit increase of

$PM_{2.5}$ in $\mu g/m^3$. The relationships were unaffected by the inclusion of weather variables such as temperature, wind speed, and dew point.

Pope et al. (1991) studied pulmonary function (PEFR) in asthmatic school children in the Utah Valley. The group of participants was selected from 4th and 5th grade elementary students in 3 schools in the immediate vicinity of PM_{10} monitors operated by the Utah State Department of Health in Orem and Lindon, UT. PM_{10} values for 24-h samples collected from midnight to midnight ranged from 11 to 195 $\mu g/m^3$. There was limited monitoring of SO_2, NO_2, and O_3. Participants were restricted to those who responded positively to one of: ever wheezed without a cold, wheezed for 3 days out of a week for a month or longer or had a doctor say the "child has asthma". This resulted in 34 subjects being included in the final analyses. PEFR values were averaged across participants, and the deviations were analyzed using single period and polynomial-distributed lag models. The estimated coefficient for PM_{10} was -0.0110 l/min (0.0082). This coefficient corresponds to a 9.2 ml/s decrease in PEFR for a 50 $\mu g/m^3$ increase in PM_{10}. This effect was not statistically significant, but using a five day moving average of PM_{10} did result in a significant regression coefficient. The relationship was not affected by the inclusion of low temperature as a covariate.

Pope et al. (1991) also studied pulmonary function (PEFR) in asthmatics aged 8 to 72 in the Utah Valley, selected from those referred by local physicians. This resulted in 21 subjects being included in the final analysis. PM_{10} monitors operated by the Utah State Department of Health collected 24 h samples from midnight to midnight (PM_{10} range 11 to 195 $\mu g/m^3$). There was limited monitoring of SO_2, NO_2, and ozone. PEFR values were averaged across participants, and the deviations were analyzed using single period and polynomial-distributed lag models. The estimated coefficient for PM_{10} was -0.0175 l/min (0.0092), corresponding to a 14.6 ml/s decrease in PEFR for a PM_{10} 50 $\mu g/m^3$ increase. This effect was not statistically significant, but using a five day moving average of PM_{10} did result in a significant regression coefficient. The relationship was not affected by the inclusion of low temperature as a covariate.

Pope and Dockery (1992) also studied non-asthmatic symptomatic and asymptomatic Utah Valley children selected from 4th and 5th grade elementary students in the three schools near PM_{10} monitors in Orem and Lindon, UT. Of 129 children identified by questionnaire as being mildly symptomatic, 60 were selected; and 60 more with no symptoms were selected. The subjects were followed from December 1, 1990 to March 15, 1991. Utah State Department of

Health PM_{10} monitors collected 24 h samples from midnight to midnight; PM_{10} ranged from 7 to 251 $\mu g/m^3$. For purposes of analyses, five day moving averages of PM_{10} were used for exposure estimates. Limited monitoring of SO_2, NO_2, and O_3 was conducted. Mean deviations of PEF were computed for each individual. Weighted least squares regression found a minus 0.00060 (0.00020) change in PEF per $\mu g/m^3$ PM_{10} in symptomatic children and a minus 0.00042 (0.00017) change in PEF per $\mu g/m^3$ PM_{10} in asymptomatic children. No relationship between low temperature and PEF was found.

Koenig et al. (1993) studied two groups of elementary school children, one during the school year 1988 to 1989 and another during the school year 1989 to 1990. The subjects in the first study included 326 children, 24 of whom were asthmatics. During the second year, only 20 asthmatics were studied (14 of which were in the original study). The FVC and $FEV_{1.0}$ were measured for each child in September, December, February, and May of each year. Fine particles, considered to be the primary pollutant of interest, were measured by nephelometer, with 12-h averages (7:00 PM to 7:00 AM) being used as the exposure measure. Additional information on $PM_{2.5}$ was collected and shown to be linearly related to light scattering (r^2 = 0.945). A mixed model was used to analyze the data. The model included random effects terms for the individuals and fixed effects terms for height, temperature, and light scattering. No relationship was found between light scattering and lung function in the larger sample, but a significant relationship was found in the asthmatics. When converted to $PM_{2.5}$ units, the decrease in $FEV_{1.0}$ was minus 0.0017 (0.0006) liters/($\mu g/m^3$). Effects of other pollutants were not considered.

Silverman et al. (1992) studied 36 asthmatic children over a 10-day period in the summer and a 10-day period in the winter in Toronto, Canada. Subjects in the first study (17 subjects) and in the second (19 subjects) were selected from a pool of 800 asthmatic children from the Gage Research Institute in Toronto. Patients were selected if they had a diagnosis of asthma and experienced wheezing at least a few times a week. Lung function measurements were obtained at the start and end of each day. Subjects carried a portable monitor which measured PM, SO_2, and NO_2. The first study measured particles less then 25 microns, the second less than 10 microns. The regression coefficient of $FEV_{1.0}$ on PM was -0.78 ml/($\mu g/m^3$) for the summer and 0.18 ml/($\mu g/m^3$) for the winter for Study 1, and −1.65 and 2.83 ml/($\mu g/m^3$) for the summer and winter in Study 2. No standard errors were given. The SAS analysis procedure was not

specified, and there was no mention of a repeated measures design. Results were not reported for SO_2 and NO_2 as exposure variables.

Hoek and Brunekreef (1993) studied pulmonary function in 112 children aged 7 to 12 residing in a non-urban area near Wageningen, NL. Spirometry was performed every three weeks for a total of six times; and one more measurement was made during an air pollution episode. PM_{10} was measured daily (3PM to 3PM) with an instrument similar to the Sierra Anderson 241 dichotomous sampler. SO_2 was measured by fluorescence and NO_2 by chemiluminescence. Linear regression analysis using the SAS procedure AUTOREG yielded an estimated coefficient for FEV_1 with PM_{10} of -0.55 ml/($\mu g/m^3$) (0.10) and for PEF of -0.82 (ml/s)/($\mu g/m^3$) (0.50). Lagged PM_{10} values gave similar coefficients. SO_2 and black smoke coefficients were similar in magnitude. Thus, both FEV_1 and PEF showed decreases related to pollution measures, but it was not possible to seperate out effects of one or another pollutant.

Hoek and Brunekreef (1994) studied pulmonary function and respiratory symptoms in Dutch children aged 7 to 11 in the towns of Deurne, Enkhuizen, Venlo, and Nijmegen, NL. Each child was studied six to ten times during one of three winters (1987/88, 1988/89, 1989/90). Measurements of FEV were obtained along with information on respiratory symptoms. PM_{10} was measured daily (3 pm to 3 pm), as were SO_2 and NO_2. Linear regression analysis using the SAS procedure MODEL with the %AR macro was used. The estimated coefficient for FEV_1 with PM_{10} was -0.10 ml/($\mu g/m^3$) (0.06) and the estimated coefficient for PEF was −0.82 (ml/s)/($\mu g/m^3$) (0.29). Lagged PM_{10} values gave similar coefficients. PM_{10} and NO_2 coefficients remained significant after adjusting for ambient temperature, but pollutants such as SO_2, HONO, sulfate and nitrate did not. Other adjustments for factors such as relative humidity, self-reported colds, and learning effects did not affect magnitudes of estimated coefficients.

Lebowitz et al. (1992) studied 30 children with a current diagnosis of asthma using PEFR measurements twice daily. A total of 674 PEFR measurements were analyzed, and information on individual activity patterns was collected. $PM_{2.5}$ and PM_{10} samples were collected in 50% of the homes. Six local monitoring stations were used to measure outdoor exposure. Using a random effects model, PEFR was found to be significantly lower in the morning for children who lived in homes with higher PM concentrations.

Johnson et al. (1982) studied lung function in children as part of the Montana Air Pollution Study, designed to collect sequential pulmonary function data on children from November 1979

to April 1980 at six different time points. By adding a 7th round of testing on May 23, 1980, the study took advantage of the natural experiment created by the eruption on May 18, 1980 of the Mt. St. Helens volcano in Washington state. About 100 children had been measured for FVC, $FEV_{1.0}$, and FEF_{25-75} on six earlier occasions. During five of these measurement periods the 3-day TSP average was relatively low (98 to 154 $\mu g/m^3$), but in one period, the average was 440 $\mu g/m^3$. The eruption of the volcano on May 18, 1980 forced nearly everybody indoors for the following three days. Most children who ventured out did so with masks on. By May 23, the air had cleared enough so that children returned to school, and their pulmonary function was measured. The TSP values for the four preceding days ranged from 948 to 11,054 $\mu g/m^3$. The authors used an unusual method of analysis, described in the appendix of their report. Interestingly, there was a larger decrease in lung function on the 400 $\mu g/m^3$ day than there was on the day following the high volcanic ash episode.

Johnson et al. (1990) studied pulmonary function in 120 3rd and 4th grade children in Missoula, MT during 1978 to 1979 who were tested up to six times between October 1978 and May 1979. FVC, $FEV_{1.0}$, and FEF_{25-75} were measured. TSP was monitored daily near the center of the study area. RSP was measured every third day and estimated from TSP and other variables on the other days. The average of the current day's and the previous two day's pollution was used as the estimate of exposure. Each child who had at least three readings was used as his own control. Percent changes in FVC, $FEV_{1.0}$, and FEF_{25-75} on higher pollution days as compared with the same measurements on days with lower pollution exposure were used as the response variable. FVC averages were decreased about 0.40% on days with RSP 31 to 60 $\mu g/m^3$ and decreased about 0.75% on days with RSP > 60 $\mu g/m^3$. Similar but smaller changes were seen in $FEV_{1.0}$ and FEF_{25-75}. All changes were marginally significant. No other pollutants were mentioned.

Roemer et al. (1993) studied Dutch children with chronic respiratory symptoms. Parents of children in grades 3 to 8 in two small nonindustrial towns in the Netherlands were given questionnaires about respiratory symptoms. Of the 313 children with positive responses for cough or shortness of breath (S.O.B), 74 were included in the study. Peak flows were measured in the morning and evening. PM_{10} was measured daily using an Anderson dichotomous sampler. Black smoke (BS), SO_2, and NO_2 were also measured. Regression coefficients for both morning and evening current day's PM_{10} levels were significant, but lagged PM_{10} values were not. The

coefficient for current day's PM_{10} with morning PEF was -0.90 (ml/s)/($\mu g/m^3$) (0.28). Evening peak flow, but not morning peak flow, was also significantly related to SO_2; BS, however, was not related to peak flow.

Studnicka et al. (1995) studied acidic particles in a summer camp study in southern Austria between June 28 and August 28, 1991. Daily spirometry was measured in three panels of children age 7 or older, for a total of 133 subjects. On site measurements were taken for PM_{10}, H^+, sulfate, ammonia, and ozone. A repeated measures linear regression model was fitted using a SAS macro. Pulmonary function measurements made by a rolling-seal-type instrument (which gave flow-volume tracings) yielded $FEV_{1.0}$, FVC, and PEFR data. The results from all three panels combined suggested that PM_{10} was marginally related to a decrease in $FEV_{1.0}$, but was less related to FVC and PEFR. Results for H^+ are discussed in Section 12.5. The coefficient for FVC suggested that an increase of 50 $\mu g/m^3$ in PM_{10} was associated with a 66 ml (39) decrease in FVC and a 99 ml/s (99) decrease in PEFR.

Neas et al. (1995) studied peak expiratory flow rates in 83 children in Uniontown, PA. PEFR rates were measured over an 87 day period during summer 1990, using a Collins recording survey spirometer. Air pollution data was collected from a monitoring site located 2 km north of the center of the town, and included PM_{10}, $PM_{2.5}$, ozone, SO_2, sulfate fraction, and H^+. The $PM_{2.5}$ values had a mean of 24.5 $\mu g/m^3$ and an interquartile range of 18.9. The PEFR values were analyzed using the autoregressive integrated moving average procedure of SAS. The model included terms for temperature, time trend, and second-order autocorrelations. The largest decreases in PEFR were related to H^+, but they were also related to both $PM_{2.5}$ and ozone.

Studies of Pulmonary Function in Adults

Pope and Kanner (1993) studied adults in the Salt Lake Valley, using spirometric data from the NHLBI-sponsored Salt Lake City Center of the Lung Health Study. Based on presence of mild COPD and willingness to participate in a 5-year smoking cessation study, 624 participants were selected. Analyses were based on two initial screening visits before randomization into the NHLBI Study; 399 subjects had adequate data to be in the analyses. PM_{10} monitors operated by the Utah State Department of Health collected 24-h samples

midnight to midnight. Limited monitoring of SO_2, NO_2, and O_3 showed these pollutants to always be well below their respective NAAQS, and none were included in the analyses. Regression analyses for change in FEV_1 (liters) per change in PM_{10} ($\mu g/m^3$) found a coefficient of -0.58 ml/($\mu g/m^3$). Changes were also seen in the ratio of FEV_1 to FVC, but PEF was not measured.

Dusseldorp et al. (1994) studied pulmonary function in 32 adults living near a large steel plant in Wijk aan Zee, NL. During the study period, PM_{10} levels ranged from 36 to 137 $\mu g/m^3$. Peak flow measurements (PEFR) were measured twice daily using a Mini Wright peak flow meter. Diary information on acute respiratory symptoms, medication use, and presence of fever was also collected. The study was conducted from 11 October 1993 to 22 December 1993, and the average number of days per subject was 66. Multiple linear regression analysis with adjustment for first order autocorrelation. The regression coefficient for evening PEFR on PM_{10} (lag zero) was -0.90 (ml/s)/$\mu g/m^3$ (0.36), and for morning PEFR on PM_{10} (lag zero) it was -1.53 (ml/s)/$\mu g/m^3$ (0.43). These correspond to estimated decreases in PEFR per 50$\mu g/m^3$ PM_{10} increase of 45 and 77 ml/sec respectively. Lags of one, two, and three days were also fitted, but gave smaller estimated coefficients.

Perry et al. (1983) conducted a longitudinal study of 24 Denver area asthmatics' pulmonary function, symptoms, and medication use followed daily January through March, 1979. Peak flows (from Mini-Wright Peak Flow Meters), symptoms, and medication use were measured twice a day. Fine and coarse PM mass (as well as sulfate and nitrate fractions) were available from an east and a west Denver site, and CO, SO_2, and O_3 were all also measured. Dichotomous, virtual impactor samplers provided daily measurements of thoracic PM (total mass, sulfates, and nitrates), for coarse (2.5 to 15 μm) and for fine fractions (<2.5 μm), with all PM measures being relatively low during the study.

Temperature and barometric pressure were also measured. Individual subject data were analyzed separately by regression analysis. The coefficients were then tested using a non-parametric Wilcoxon signed rank test. None of the PM measures were associated with changes in any of the health endpoints. This study had very low power, given the small sample size and lack of high PM levels.

Acute Pulmonary Function Studies Summary

Pulmonary function results are slightly easier to compare because most studies used peak flow (PEFR) or forced expiratory volume (FEV) as the health end-point measure. The acute pulmonary function studies (summarized in Table 12-13) are suggestive of a short term effect resulting from PM pollution. Peak flow rates show decreases in the range of 30 to 40 ml/sec resulting from an increase of 50 µg/m^3 in PM_{10} or its equivalent (see Figure 12-6). The results appear to be larger in symptomatic groups such as asthmatics. The effects are seen across a variety of study designs, authors, and analysis methodologies. Effects using FEV_1 or FVC as endpoints are less consistent. For comparison, a study of over 16,000 children found that maternal smoking decreased a child's FEV by 10 to 30 ml (Hasselblad et al., 1981).

Pope and Kanner (1993) provided one estimate of the effect of PM on pulmonary function in adults. They found a 29 (±10) ml decrease in FEV_1 per 50 μg/m^3 increase in PM_{10}, which is similar in magnitude to the changes found in children. Dusseldorp et al. (1994), in comparison, found 45 and 77 ml/sec decreases for evening and morning PEFR, respectively, per 50 μg/m^3 increase in PM_{10}.

12.4 HEALTH EFFECTS OF LONG-TERM EXPOSURE TO PARTICULATE MATTER

12.4.1 Mortality Effects of Long-Term Particulate Matter Exposures

The long-term effects of air pollution may be examined by considering gradual changes over time (the longitudinal study) or by contrasting spatial differences at a given point in time (the cross-sectional study). Longitudinal studies examine the effects of long-term changes in air quality, such as those that accompany pollution abatement campaigns. Only a

TABLE 12-13. ACUTE PULMONARY FUNCTION CHANGES

Study	PM Type & No. Sites	PM Mean & Range‡	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Dockery et al. (1982), school age children in Steubenville, OH, measured at three times between 1978 and 1980	Single station measuring TSP	Up to 455 $\mu g/m^3$ No means given	Individual regression analyses for each child, coefficients pooled across time	SO_2	Average temperature	TSP	FVC: 8.1 ml; $FEV_{0.75}$: 1.8 ml. Note: decreases were statistically significant
Dassen et al. (1986), school age children in The Netherlands, measured in November, 1984 and January, 1985	Six station network measuring TSP, RSP (PM_{10})	TSP and RSP both exceeded 200 $\mu g/m^3$ No means given	Multiple linear regression	SO_2	Technician, appliance, presence of colds	RSP	Slopes not given but FVC, FEV,, and PEFR were all significantly reduced during episodes
Quackenboss et al. (1991), asthmatic children aged 6 to 15 years in Tuscon, AZ, measured in May and November, 1988	Individual monitoring in homes of $PM_{2.5}$, PM_{10}		Random effects linear model	NO_2	Temperature, wind speed, dew point	$PM_{2.5}$	PEFR: 375 ml/s Note: these are diurnal rather than daily changes
Pope et al. (1991), study of asthmatic children in the Utah Valley	PM_{10} monitors in Orem and Lindon, Utah	PM_{10} ranged from 11 to 195 $\mu g/m^3$	Weighted least squares regression	SO_2, NO_2, ozone	Low temp.	PM_{10}	PEFR: 55 ml/s (24, 86)
Pope and Dockery (1992), study of non-asthmatic symptomatic and asymptomatic children in Utah Valley, UT	PM_{10} monitors in Orem and Lindon, Utah	PM_{10} ranged from 7 to 251 $\mu g/m^3$	Weighted least squares regression	SO_2, NO_2, ozone	Low temp.	PM_{10}	Symptomatic PEFR 30 ml/s (10, Asymptom. PEFR 21 (4, 38 ml/s)

TABLE 12-13 (cont'd). ACUTE PULMONARY FUNCTION CHANGES

Study	PM Type & No. Sites	PM Mean & Range‡	Model Type & Lag Structure	Other Pollutants Measured	Weather & Other Factors	Pollutants in Model	Decrease* (Confidence Interval)
Koenig et al. (1993), study of asthmatic and non-asthmatic elementary school children in Seattle, WA in 1989 and 1990	$PM_{2.5}$ calibrated from light scattering	$PM_{2.5}$ ranged from 5 to 45 µg/m^3	Random effects linear regression	none	height, temperature	$PM_{2.5}$	Asthmatics FEV_1 42 ml (12, 73 ml) FVC 45 ml (20, 70 ml) Non-asthmatics FEV_1 4 ml (-7, 15 ml) FVC -8 ml (-20, 3 ml)
Hoek and Brunekreef (1993), study of children aged 7 to 12 in Wageningen, Netherlands	Single site measure black smoke. PM_{10} was measured during episodes	PM_{10} range of 30 to 144 µg/m^3	SAS procedure AUTOREG	SO_2, NO_2	day of study	PM	$PEFR_{10}$ 41 ml/s (-8, 90)
Roemer et al. (1993), study of children with chronic respiratory symptoms in The Netherlands	Single site measure black smoke. PM_{10} was measured using an Anderson dichot	PM_{10} range 30 to 144 µg/m^3	multiple linear regression analysis	SO_2, NO_2	none	PM_{10}	PEFR 34 ml/s (9, 59)
Pope and Kanner (1993), study of adults in the Utah Valley from 1987 to 1989	PM_{10} was collected daily from the north Salt Lake site	PM_{10} daily mean 55 µg/m^3, range 1 to 181 µg/m^3	Linear regression on difference in PFT as a function of PM_{10}	Limited monitoring of SO_2, NO_2, and ozone	low temperature	$PM_{2.5}$	FEV_1 29 ml (7, 51 ml) FVC 15 ml (-15, 45 ml)
Neas et al. (1995), study of 83 children in Uniontown, PA, in the summer of 1990	One site mean 2 km north of center of town; measured $PM_{2.5}$ and PM_{10}	Mean PM_{10} 36 μg/m^3 max. 83 μg/m^3 Mean $PM_{2.5}$ 25; max. 88 μg/m^3	Autoregressive liner regression model	O_3, SO_2, sulfate, H^+	Temperature	None	PEFR per 25 μg/m PM : 23.1 (-0.3 to 36.9 ml)

TABLE 12-13 (cont'd). ACUTE PULMONARY FUNCTION CHANGES

Study	PM Type & No. Sites	PM Mean & Range‡	Model Type & Lag Structure	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Studnicka et al. (1995), study of 133 children at a summer camp in southern Austria in 1991	One site located at the camp measured PM_{10}	Means by time period ranged from 6.6 to 10.7 $\mu g/m^3$	Linear regresison with repeated measures	H^+, SO_2, ammonia	Temperature, humidity, pollen, gender, height, age	H^+	FVC 17.5 ml (-64.0, 99.0) FEV_1 66.5 ml (-10.0, 143.0) PEFR 99 ml/s
Hoek and Brunekreef (1994), study of children in 4 towns in The Netherlands	No. of sites not given 24-h PM_{10} measured	Mean PM_{10} 45 $\mu g/m^3$, range 14-126 $\mu g/m^3$	Box-Jenkins first order autoregressive model	SO_2, NO_2, sulfate, nitrate, HONO	Minimum temperature	None	FVC -0.5 ml (-3.5, 2.5); FEV_1 5.0 ml (-1.0, 11.0) PEFR 41.0 ml/sec (12.5, 69.5)
Dusseldorp et al. (1994), study of 32 adults in a steel plant in Wijkaan Zee, The Netherlands	PM_{10} measured at 3 sites	PM_{10} mean 54 $\mu g/m^3$, range 4-137 $\mu g/m^3$	Multiple linear regression with first order autocorrelation	Iron, Mn, sodium, silicon	Wind direction, temperature	Iron	PEFR evening 45 ml/sec (9, 81) PEFR morning 77 ml/sec (34, 119)

*Decreases in lung function calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.
‡Means and Ranges listed if reported by authors.

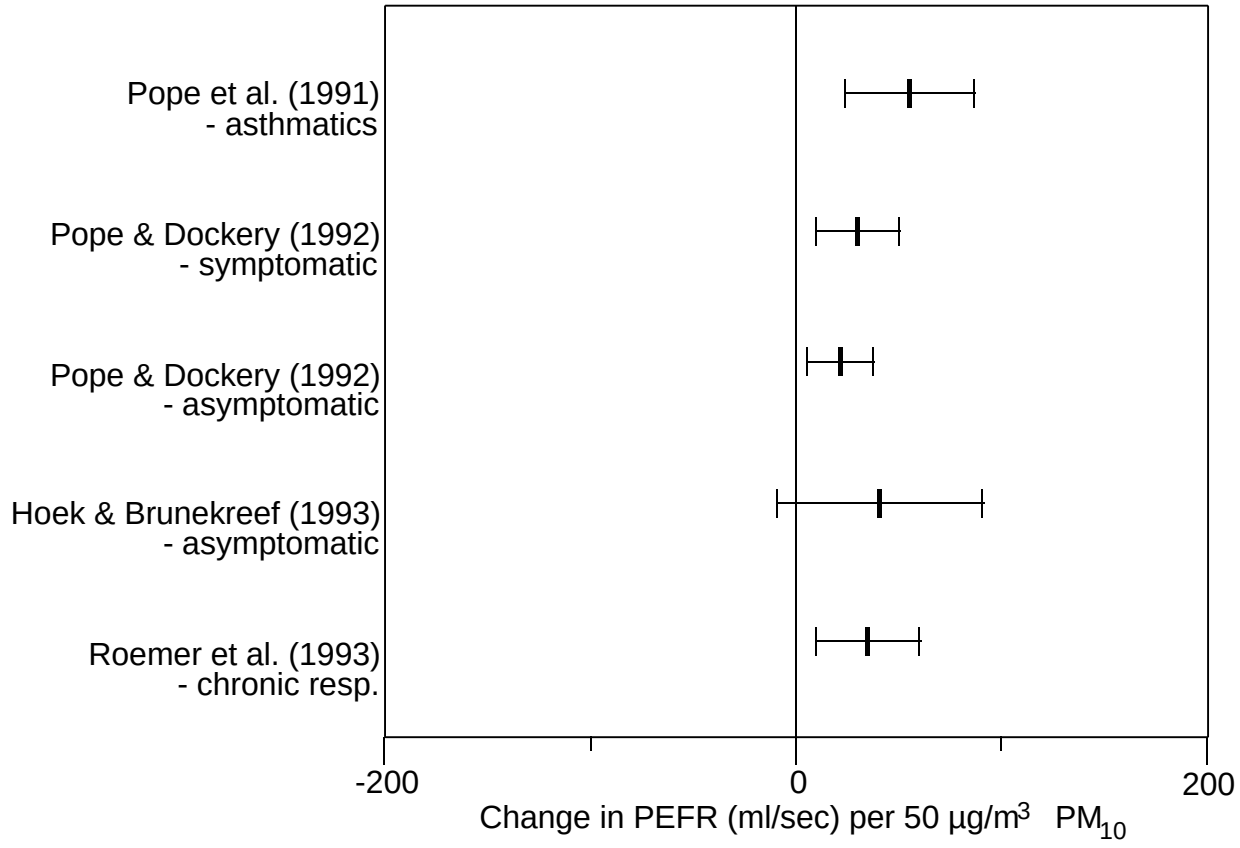

Figure 12-6. Selected acute pulmonary function change studies showing change in peak expiratory flow rate (ml/s) per 50 μg/m^3 PM_{10} increases.

few such studies have been published (Lipfert, 1994a); none recently. Cross-sectional studies are designed to infer the accumulated long-term effects of the environment by contrasting spatial differences. As with all epidemiology, such spatial gradients may only be credibly attributed to air quality after the potential confounders have been controlled.

Mortality rates or probabilities of survival may differ by location for any of a number of reasons. Long-term health risk factors may be further subdivided into factors that relate to the population of a given place (age, race, education, lifestyle, for example) and factors that relate to the physico-chemical environment of that place (climate, air and water quality). There are also likely to be interactions between these two subcategories, since places with desirable environments may attract as in-migrants that portion of the population that is better off economically while the disadvantaged part of the population may be forced to remain in less desirable locations and in those with depressed economies.

Annual mortality rates must also reflect the net sum of acute events that took place that year (Evans et al., 1984a). If the increases in daily death rates associated with acute events are not subsequently canceled by decreases (a phenomenon referred to as "harvesting"), annual rates will indicate the history of these acute effects. Thus, differences in long-term mortality rates associated with air pollution are likely to reflect some combination of acute and chronic effects. Although both types of information are useful contributions to the overall understanding of the health effects of air pollution, their distinction may be difficult if based on statistical criteria alone.

Long-term mortality studies are considered here in two groups:

1. Cross-sectional studies based entirely on the characteristics of groups averaged across various geopolitical units, referred to as population-based studies.

2. Prospective cohort studies based on (a) health and demographic data for individuals and (b) air pollution exposure data were based on community-wide averages in much the same way as the population-based studies.

None of the studies available for review had individual data on personal exposures to air pollution. The population-based studies used annual mortality rates and annual average air quality data, usually for coincident periods centered on decennial census years. Brief considerations have been given to exposures lagged by 10 or more years in several instances, in an attempt to deduce effects of exposures over longer periods. The prospective studies consider the net survival rates over a multi- year period of follow-up; various assumptions were made by the different investigators about the appropriate timing of air pollution exposures. The studies thus varied in terms of their ability to provide either a measure of lagged chronic effects or an integrated measure of acute effects during a given period.

12.4.1.1 Methodological Considerations

Methods for cross-sectional analysis were considered in a general way in the Methodology discussion (Section 12.2). However, there are some specific guidelines that should be considered with respect to the estimation of long-term effects on the basis of spatial gradients. In general, the most difficult problems are (1) collinearity among pollutants, (2) variable and inadequate characterizations of pollutant exposure, and (3) confounding by non-pollutant variables.

However, these issues are somewhat different than those encountered in the acute mortality and morbidity studies. Collinearity between PM and some pollutants may be less of a problem because of differences among regions in typical pollution sources, with sulfur oxides a relatively more important factor in eastern communities and nitrogen oxides relatively more important in western communities. On the other hand, with multiple years of pollutant data collected on a daily or every-sixth-day schedule, it may be possible to construct a variety of different pollution exposure indices from the same data base, with different indices more or less correlated in any analysis. The second concern is that of adequately characterizing long-term exposures, with choices of long-term averages, current year averages, or moving averages lagged by years rather than days, seasonal weights, etc. The third problem, confounding by other factors, now includes demographic differences among communities that may affect baseline mortality rates, and also change over time.

The study of long-term or chronic health effects of air pollution began with population-based studies and became fraught with difficulty and controversy, more so than the short-term studies (Smith, 1975; Lipfert, 1980a; Ware et al., 1981; Ricci and Wyzga, 1983; Evans et al., 1984b). The primary method of analysis involves comparing the health statistics of populations of places which have had different environments over the long-term. However, the comparisons are often complicated or even compromised by other differences that may be related to the sources and effects of air pollution, such as industrialization or climate. Cross-sectional studies often use data from only one specific year that may or may not be truly representative of long-term environmental conditions.

The most recent contributions to this literature have involved prospective survival analysis of defined cohorts. These studies offer the potential of much more credible results because of their ability to draw upon individual characteristics such as smoking status. Stratification effectively reduces any uncertainties as to whether a potential confounder has been adequately controlled.

Example of Spatial Confounding

Some air pollution indices such as sulfates appear to have substantial potential for confounding, because they are collinear with several important socioeconomic indicator variables

that relate to the geographic concentration of both the air pollutant and the covariate in various parts of the country. For example, regression analysis of 1980 SMSA data (Lipfert, 1992) has shown that the migration variable, defined here as the percentage change in SMSA population from 1970 to 1980, is one of the most important potential confounders for sulfate. When migration is included in a regression for all-cause or cardiovascular mortality, neither SO_4^{2-} nor immigration are statistically significant predictors. Thus, separating the effects of these two collinear variables is critical in estimating the mortality response to sulfates or other air pollutants.

Additional reanalyses of data reported on by Lipfert (1992) for this document further evaluated impacts of migration as a potential confounders in long-term PM exposure studies. The 149 SMSAs were trichotomized by migration tertiles: SMSAs with less than 4.5% population gain, SMSAs with gains from 4.5 to 15%, and SMSAs with more than 15% gain. Cross tabulations showed the following variables be monotonic across these divisions:

- variables that increased with population gain (% black, % poor, % with college education, % other nonwhite, annual average Pb concentration);
- variables that decreased with population gain (mortality rates for all causes and for major cardiovascular causes, degree days, median age, % over 65, concentrations of SO_2, SO_4^{2-}, NO_x, $PM_{2.5}$, Mn).

This suggests that the migration variable might act as a delineator between northern "rustbelt" locations with shrinking economies and southern and "sunbelt" locations with growing economies. Studies on individuals have shown that selective migration can have an effect on the health status of a community, which is what is being analyzed in a population-based study. As noted previously, other sociodemographic variables can also be confounded with location, such as the correlation of high percentages of Hispanic residents with high TSP concentrations in the southwestern states.

Regression analyses involving these variables showed the following:

(a) Substituting the trichotomized migration variable for the continuous measure of population change shifted the mortality response from population change to sulfate: the OLS coefficient increased from 0.028 (s.e. = 0.016) to 0.045 (s.e. = 0.016). This is an example of how an incomplete specification for a confounder can increase the apparent response for the "confoundee" without inflating its standard error (the classic symptom of collinearity).

(b) Stratifying by the 3 levels of migration showed that the continuous population change variable remained significant in all 3 levels, while SO_4^{2-} was only significant in the two strata with smaller population gains. Stratifying by SO_4^{2-} (two levels) showed that SO_4^{2-} was a significant (positive) predictor of mortality only in the higher stratum (with or without the population change variable), while population change was consistently significant in both strata.

Figure 12-7 extends this analysis to $PM_{2.5}$, for a smaller number of locations. Here the slope reduction due to introducing additional nonpollution variables is less dramatic but still notable. Figure 12-7a shows the regression model for 62 SMSAs when only age and race are used as covariates; here, a strong positive relationship between $PM_{2.5}$ age- and race-adjusted mortality is evident. When mortality is also adjusted for smoking , education, overweight, ethnicity, water hardness, sedentary lifestyle, poverty, and migration (Figure 12-7b,) the strength of the relationship with $PM_{2.5}$ decreases (but is not eliminated) and residual variability is significantly reduced. Thus, confounding by covariates such as migration merely reduced the effect size estimate for fine particles, but markedly diminished the relationship between sulfates and mortality.

Spatial Patterns in the United States

Spatial patterns of U.S. mortality rates show some well-defined trends that have existed for decades (Lipfert, 1994a). Such patterns are sometimes called the "geography of disease." In general, heart disease is higher east of the Mississippi and ischemic heart disease shows even sharper gradients and peaks in the Northeast (part of this gradient could be due to differences in diagnostic practices, although cold weather has also been implicated. Pneumonia and influenza deaths are generally well distributed across the country but tend to be higher north of about the 36th parallel. In contrast, the "stroke belt" has been defined as a broad east-west stripe across the southern part of the United States.

Spatial trends in air pollution have both local and regional patterns. Local patterns within cities reflect the presence of primary pollutants from local sources (CO from traffic, particles from industrial operations, SO_2 and NO_2 from combustion sources, for example).

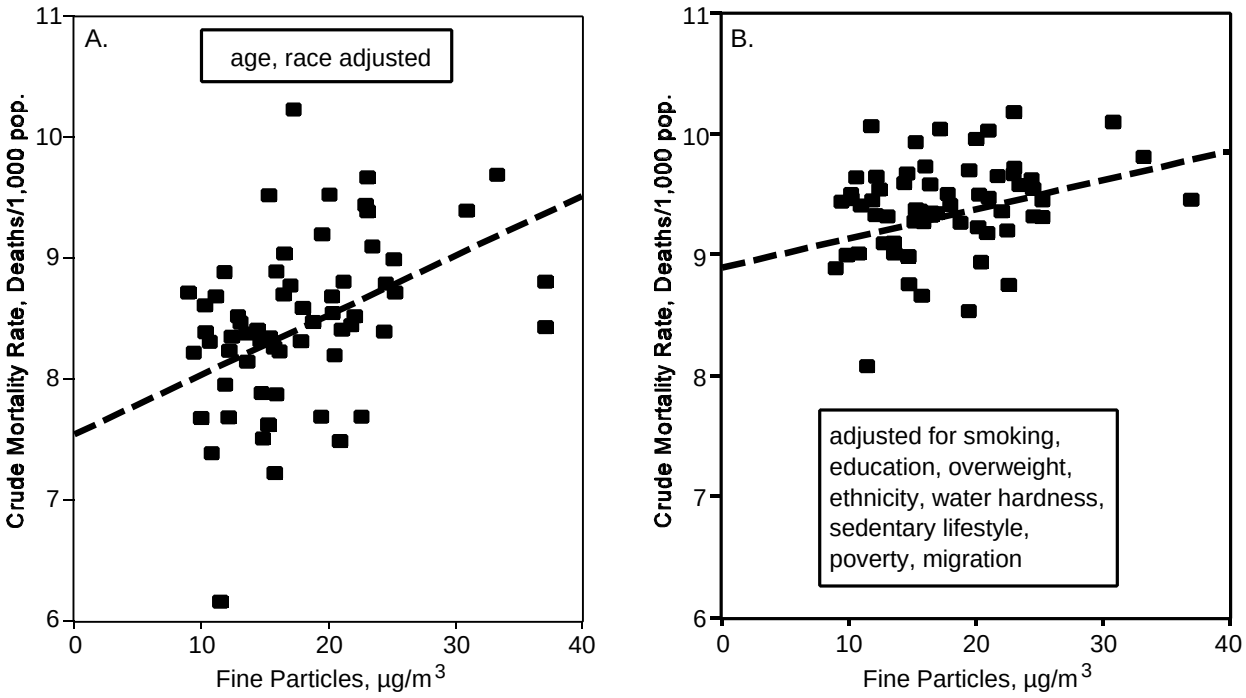

Figure 12-7. Effect of confounding on $PM_{2.5}$-mortality relationship in 1980 SMSA data. The $PM_{2.5}$ effect on mortality is reduced (but not eliminated) by the introduction of numerous potentially confounding variables (e.g., smoking, migration, etc.) into regression analyses as shown in Panel B in comparison to analyses only including age and race adjustments illustrated in Panel A.

Source: U.S. EPA reanalysis of data reported by Lipfert (1992).

There are also multi-state regional patterns in secondary pollutants, such as sulfates and other fine particles in Appalachia and the east north central "rust belt," and ozone in Southern California and along the Northeast corridor from Washington to Boston. Collinearity among pollutants results from common spatial patterns of their major sources.

The possibilities for confounding by regional factors vary with the scale of the analysis; comparisons within regions may thus be less susceptible than comparisons across the whole country. For this reason, consistency between different types of studies becomes very important in considering causality.

Risk Measures

Most of these studies consider deaths from all causes. Some of them subtract deaths due to accidents, homicides, and suicides, yielding a quantity referred to by various authors as "nonexternal" deaths, "deaths from all natural causes," or "all-disease deaths." Measures of the risks attributed to air pollution differ by type of study and regression model. Some studies report relative risks (mortality ratios) associated with specified but arbitrary pollution "reference" levels, such as 100 $\mu g/m^3$ of particulate matter or 50 ppb of ozone. These figures are obtained by multiplying the regression coefficient (the relative risk per unit of pollution) times the desired pollution level. This practice is convenient for comparing studies of the same pollutant but is less suitable for comparing the relative effects of different pollutants, because the actual relationship between pollutants in a given city may not correspond with that assumed by the reference levels. Others report ordinary least-squares regression coefficients in the original units of the study, such as change in annual death rate per unit of pollution. These coefficients are specific to the measures used for both dependent and independent variables, but may be converted to approximate log-linear coefficients or relative risk by dividing by the mean value of the dependent variable.

One measure that is free of measurement units is the "elasticity," a term taken from economics defining a nondimensional regression coefficient of y on x_i (at the mean) as

$$e_i = b_i \, x_i/\overline{y} \qquad (12.4.1\text{-}1)$$

Elasticities may be expressed as decimals or in percent and offer another measure of attributable risk, based on the mean values of the x_i. An elasticity of 0.04 thus corresponds to a relative risk of 1.04 at the mean pollution level. Comparison of two elasticities may be misleading if the mean values differ widely. Note that when the "effect" of a variable ($b_i x_i$) is expressed as a percentage of the mean total response, "effect" and elasticity are synonymous.

Model Specifications for Long-term Mortality Studies

Because of the large number of potential confounding variables in spatial analysis, multiple regression has been the statistical method of choice. Some epidemiological studies have included the effects of both air quality and drinking water quality (mainly water hardness; see Pocock et al., 1980, for example). Models for population studies may be either linear or log-linear, and some investigators have included pollutant thresholds using piecewise linear models. For population-based studies, the dependent variable is usually an annual mortality rate for the geographic unit in question. It can be argued that, if age adjustment is used for the dependent variable, it must also be used for any independent variable that may also exhibit age dependency (such as smoking or air pollution exposure) but this has generally not been done.

Prospective studies of individuals have featured the proportional hazards model, in which the risk factors are multiplicative (these coefficients correspond to elasticities). The dependent variable is thus dichotomous (alive or dead). The range in survival probability among adult individuals is quite large, encompassing more than two orders of magnitude in mortality rate, as a function of age and other individual risk factors. Years of medical research have identified some of these risk factors as genetic predisposition, exposure to infectious diseases, access to medical care, and personal lifestyles (including diet, exercise, and smoking habits).

In contrast, the variability among cities and Standard Metropolitan Statistical Area (SMSA) mortality rates is relatively modest, with a coefficient of variation (CV) of about 17% (Lipfert, 1993), most of which is due to differences in age distributions. This corresponds to a standard deviation in average longevity of only about 21 mo. This reduction in variability occurs because areas as large as SMSAs in the United States tend to be similar in terms of their average characteristics, especially within regions; i.e., most of the variability among individuals is "averaged out" by working with city-wide averages. It is thus much easier to accurately predict the death rate when it is averaged over some geopolitical unit than it is to predict the survival of an individual within some specified time period. In any case, the ability to accurately predict the effects of exposure to air pollution depends on the validity of the model. Unfortunately, it is unavoidable that all such models are incomplete and thus may contain the potential for bias (Cohen, 1994).

As discussed above in Section 12.2, in order to confound, a variable must be correlated with both the dependent variable and the independent variable of interest. This limits consideration of confounders to established mortality risk factors that are correlated with air pollution. However, this correlation need not be direct (i.e., associated with air pollution sources per se), but, for cross-sectional analysis, the correlation is more likely to arise due to common spatial patterns, for whatever reason. Thus, sulfate is (spatially) correlated with old age, since both are most common in the Northeast and Midwest "rustbelt" area, and TSP is correlated with the presence of Hispanics, since both these factors are generally high in the Southwest. In many cases, appropriate data on confounders are not available and surrogates must be used for the actual mortality risk factors. Education is an example; staying in school longer per se does not prolong life, but better educated individuals are likely to have higher incomes and thus access to better medical care; they may also have healthier personal lifestyles. Greenland and Robins (1994a) point out, with examples, that control of potential confounders "crucially hinges on adequate measurement of the potential confounders." Klepper et al. (1993) provide other examples.

Adequately controlling for identified likely confounders is not always as straightforward as it might appear. For example, the relationship between education and health is likely to be nonlinear, as is the relationship between income and longevity (Rogot et al., 1992). Alcohol consumption and body mass are two of the risk factors that have also been shown to have non-linear relationships with mortality (see Grønbæk et al., 1994, for example). It therefore follows that the assumption of linearity may not be always be appropriate for surrogate risk factors.

State-level survey data on many other behavioral risk factors have recently become available (Siegel et al., 1993), and many of these factors are also correlated with sulfate concentrations. For example, the state-level correlation with "% 65 and over with sedentary life-style" was 0.64. The spatial collinearity between sulfate and these demographic/lifestyle factors is similar to that between daily air pollution and weather and presents a challenge to the analyst to separate cause from circumstance.

In some cases, ambient air quality monitors are sited near the locations of the worst air quality, near point sources or in the densest part of a city, in keeping with their intended regulatory function. Thus, they may overestimate the exposures of persons living in more distant

suburban areas. This is most likely to be the case for primary pollutants, such as CO, NO_2, SO_2, and PM_{10} (or TSP). The opposite may be true for some ozone monitors, because of the tendency for levels to be reduced near sources of NO. Secondary sulfate and other fine particles tend to have much longer lifetimes and thus to be more uniformly distributed over entire states or regions. Different relationships between ambient pollutant concentrations and personal exposure for different pollutants must also be considered (Chapter 7). Note that such differences in the reliability of exposure estimates will tend to bias the regression coefficients, giving an advantage to those pollutants with smoother distributions (Lipfert and Wyzga, 1995a). Because the socioeconomic characteristics of the population and, thus, their mortality risk factors are also nonrandomly distributed, especially at the local level within an SMSA, collinearity may result between their actual population exposures and these other mortality risk factors. More simply put, persons employed by a local pollution source may tend to live closer to that source, and it may thus be difficult to distinguish between their ambient exposures, their occupational exposures, and the personal characteristics that led to their employment and residence there.

Cross-sectional studies should therefore include adjustments or statisitical control of probable confounders, yet avoid overcontrol by not including variables that have only coincidental associations with no substantive basis.

12.4.1.2 Population-Based Cross-Sectional Mortality Studies

In this section, recent cross-sectional studies not reviewed in earlier documents are discussed employing averages across various geopolitical units (cities, SMSAs, etc.). No data on individuals are used; the community- based study seeks to define the (average) community characteristics that are associated with its overall average health status, in this case annual mortality rate.

Studies published after 1985 are emphasized here, but it is also useful to refer to some of the earlier influential studies for context. Table 12-14 summarizes some of the findings

TABLE 12-14. COMMUNITY-BASED CROSS-SECTIONAL STUDIES (1960 to 1974 MORTALITY)

Source	Health Outcome	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Mean City Pop.	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk[1] at TSP = 100, SO_4 = 15	RR. Confidence Interval	Elasticity
Lave and Seskin (1977) Regr. 3.3-1	Total mortality	1960, 117 SMSA, USA	TSP, min SO_4	118 4.7	(41) (3.1)	1	447,000 [2]	OLS, joint	none	none	Pct. Age 65; Pct. nonwhite; Pop. density; Pct. poor pop.	1.050 TSP 1.104 SO_4	(1.01-1.09) (1.03-1.18)	0.059 0.033
Lave and Seskin (1977) Regr. 5.2.2	Total mortality	1960, 117 SMSA, USA	TSP min SO_4	118 4.7	(41) (3/1)	1	447,000 [2]	OLS, joint	none	none	Pct. Age 65; Pct. nonwhite; Pop. density; Pct. poor pop.; Home heating fuel	1.019 TSP 1.030 SO_4	(0.98-1.05) (0.97-1.09)	0.022 0.01
Lave and Seskin (1977) Regr. 7.1-4	Total mortality	1960, 112 SMSA, USA	TSP min SO_4	95 3.5	(29) (1.9)	1	570,000 [2]	OLS joint	none	none	Pct. Age 65; Pct. nonwhite; Pop. density, Pct. poor pop.	1.091 TSP 1.129 SO_4	(1.04-1.14) (1.01-1.25)	10.087 0.030
Lipfert (1984) Regr. 4.2	Total mortality	1970, 111 SMSA, USA	TSP SO_4	96 10.9	(29) (4.5)	1	989,000	OLS, joint	none	none	Pct. Age 65; Pct. Afr. Amer.; Pct. other nonwhite; Pop. density; Pct. poor pop; adj. cig. sales, coal, wood, homeheat	1.044 TSP 1.057 SO_4	(0.98-1.07) (1.01-1.11)	0.034 0.042
Lipfert (1984) Regr. 4.7	Total mortality	1970, 69 SMSA, USA	TSP SO_4	96 10.9	(29) (4.5)	1	989,000	OLS, joint	none	O_3	Same as above, with water quality, without pop. adj.	1.052 TSP 1.035 SO_4	(0.99-1.12) (0.98-1.09)	0.054 0.026
Lipfert (1984) Tbl. 6, Line 10	Total mortality	1970, 69 SMSA	non-S TSP, SO_4	80.5 11.0	(25) (4.4)	1	989,000	OLS, joint	none	O_3	Pct. Age 65; Pct. Afr. Amer.; Pct. other nonwhite; Pop. density; Pct. poor; Pop. migration; adj. for adj. cig. sales, coal, wood, home heating, drinking water,	1.074 1.019	(1.00-1.14) NS	0.05 0.014

TABLE 12-14 (cont'd). COMMUNITY-BASED CROSS-SECTIONAL STUDIES (1960 to 1974 MORTALITY)

Source	Health Outcome	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Mean City Pop.	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk at TSP = 100, SO_4 = 15	RR. Confidence Interval	Elasticity
Chappie and Lave (1982) Regr. 2-6	Mortality from natural causes	1974, 104 SMSA	TSP SO_4	75 9.6	(41) (3.8)	1	527,000 [2]	OLS, joint[3]	none	SO_4 [3]	Pct. Age 65; Pct. nonwhite; pop. density; income;	0.99 TSP 1.23 SO_4	NA NA	-0.01 0.15
Chappie and Lave (1982) Regr. 3-6	Mortality from natural causes	1974, 102 SMSA	TSP SO_4	75 9.6	(41) (3.8)	1	527,000 [2]	OLS, joint[3]	none	SO_4 [3]	Pct. Age 65; Pct. nonwhite; pop. density; income; tobacco sales, alcohol sales; pct. college grads; industries	0.985 TSP 1.18 SO_4	NA NA	-0.015 0.12

[1]At TSP = 100 $\mu g/m^3$, SO_4 = 15 $\mu g/m^3$, concentration adjusted for migration.
[2]Median value.
[3]Regression used minimum, maximum, and mean values for TSP and SO_4 in the same model; relative risks were calculated from combined elasticity for each pollutant.

from these "background" studies, which analyzed mortality from 1960 to 1974. Studies that analyzed spatial variability in 1980 mortality are summarized in Table 12-15. Many of these studies comprise a large numbers of individual regressions; the tables indicate which ones were selected for discussion here, but the numerical column headings are more convenient for the discussion that follows.

Background and Critiques of Some Older Studies

Although there had been a few earlier intracity cross-sectional studies (Lipfert, 1994a), the current "model" for the cross-sectional population-based study was introduced by Lave and Seskin (1970, 1977). They published an extensive national cross-sectional regression analysis and concluded that about 9% of annual U.S. metropolitan mortality (ca. 1960) was associated with air pollution, considering TSP and SO_4^{2-} jointly. The analysis was based on multiple linear regression analysis of annual mortality rates in the major SMSAs in relation to coincident annual air quality levels (as measured at city centers) and to selected other explanatory variables, listed in Table 12-14. This study was the first to attempt to characterize the air pollution exposure of an entire SMSA using (often fragmentary) data from a single monitoring station. Studies by several investigators showed that the annual mean was the preferred pollution metric. As shown in the first two studies in Table 12-14, introduction of a home-heating fuel variable resulted in loss of significance and reduced relative risks for both pollution variables. There are other examples of this type of instability in Lave and Seskin (1977).

Lipfert (1984) reanalyzed Lave and Seskin's 1969 total mortality data set for 112 SMSAs (third study in Table 12-14), using corrected data and many new independent variables, including 1970 mortality to correspond better with the socioeconomic variables obtained from the 1970 Census (fourth through sixth studies in Table 12-14). The analysis was incapable of distinguishing between linear and threshold models and thus could not rule out the applicability of a threshold or piecewise linear model. A threshold for TSP was suggested at about 85 to 130 $\mu g/m^3$, and for sulfate at about 10 to 15 $\mu g/m^3$.

TABLE 12-15. COMMUNITY-BASED CROSS-SECTIONAL STUDIES (1980 MORTALITY)

Source	Health Outcome	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Mean City Pop.	Model Type	PM Lag[1] Structure	Other Pollutants	Other Factors	Relative Risk[2] at TSP = 100, SO_4 = 15	RR. Confidence Interval	Elasticity
Özkaynak and Thurston (1987) Table VI	Total mortality	1980 98 SMSA	TSP	78	(26)	1	NA	OLS sep.	none	none	Pct. age 65; median age;	1.012 TSP	(0.96, 1.06)	0.01
			SO_4	11.1	(3.4)						Pct. nonwhite; pop. density; Pct. poor, pct. w/ 4 yrs college.	1.17 SO_4	(1.09, 1.24)	0.086
Özkaynak and Thurston (1987) Table VII	Total mortality	1980, 38 SMSA	PM_{15}	38	(7.3)	1	NA	OLS sep.	none	none	Same as above.	1.059 PM	(0.95, 1.16)	0.045
			$PM_{2.5}$	20	(3.8)							1.085 $PM_{2.5}$	(0.96, 1.21)	0.068
Lipfert et al. (1988) Table 24	Total mortality	1980 172-185 cities	Fe,	1.2	(0.61)	1	57,500	OLS sep.	none	none	Pct. Age 65; birth rate;	1.044 Fe	(1.02-1.07)	0.041
			SO_4	9.5	(3.5)						Pct. Afr.-Amer; pop. density, pct. poor; Pct. pop. change; pct. w/ 4 yrs. college; Pct. Hispanic; adj. cig., sales; Pct. prior res., hard water	1.13 SO_4	(1.06-1.20)	0.071
Lipfert et al. (1988) Table 24	Total mortality	1980 68 cities	PM_{15}	38	(121)	1	57,500	OLS sep.	none	none	Same as above.	1.036 PM	NS[3]	0.027
			$PM_{2.5}$	18	(6)							1.082 $PM_{2.5}$	NS[3]	0.059
Lipfert et al. (1988) Page 60	Total mortality	1980 122 cities	TSP	88	(29)	1	about 60,000	OLS joint	10 years	none	Pct. age 65; birth rate; pct. nonwhite; pop. density; pct. poor; adj. cig. sales; pct. w/ 4 yrs. college.	about 1.0	NS[3]	NS
			SO_4	9.0	(1.8)							1.072 SO_4	(1.0, 1.14)	0.037

TABLE 12-15 (cont'd). COMMUNITY-BASED CROSS-SECTIONAL STUDIES (1980 MORTALITY)

Source	Health Outcome	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Mean City Pop.	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk[1] at TSP = 100, SO_4 = 15	RR. Confidence Interval	Elasticity
Lipfert (1993) Regr. 6.1, 6.2	Mortality from natural causes	1980 149 SMSA	TSP	68	(17)	10.6 (TSP)	928,000	OLS sep.	none	none	Pct. age 65; Pct. Afr.-Amer.; Pct. Hispanic; Pct. other nonwhite; pct. poor; pop. density; pct. pop. change; adj. cig. sales; pct. w/ 4 yrs. college; hard water, heating degr. days.	1.038 TSP	(0.97, 1.10)	0.026
			SO_4	9.3	(3.1)							1.059 SO_4	(0.99, 1.12)	0.037
Lipfert (1993) Regr. 13.1, 13.3	Mortality from natural causes	1980 62 SMSA	PM_{15}	38	(29)	1	928,000	OLS sep.	none	none	Same as above	1.036 PM	(0.98, 1.10)	0.027
			$PM_{2.5}$	18	(4.5)							1.060 $PM_{2.5}$	(0.99, 1.13)	0.043
Lipfert (1993) Regr. 9.1, 9.3	Mortality from natural causes	1980 62 SMSA	TSP	68	(17)	10.6 (TSP)	928,000	Log-linear	none	none	Same as above without other nonwhite, heating degr. days, pop. density	1.066 TSP	(1.006, 1.13)	0.044
			SO_4	9.3	(3.1)							1.021 SO_4	NS	0.012
Lipfert (1993) Regr. 13.5	Major CVD	1980 62 SMSA	SO_4 (IP)	4.3	(2.5)	1	928,000	OLS	none	none	Same as above with other nonwhite, heating degree days, pop. density	1.04 SO_4	NS	0.011
Lipfert (1993) Regr. 12.1	Major CVD	1980 62 SMSA	SO_4 (IP)	4.3	(2.5)	1	928,000	OLS	none	none	Pct. age 65; median age; pct. nonwhite; pop. density; pct., poor; pct. w/ 4 yrs coll.	1.19 SO_4	(1.03, 1.35)	0.054
Lipfert (1993) Regr. 10.3, 10.4	COPD	1980 149 SMSA	TSP-SO_4	56.4	(18)	10.6	928,000	Log-linear	none	none	Pct. age 65; pct. Afr.-Amer.; Pct. Hispanic; pop. density; pct. poor; adj. cig. sales.	1.50 TSP	(1.22, 1.83)	0.23
			TSP	68.5	(17)							1.43 TSP	(1.20, 1.71)	0.25

[1]All regression models used PM indicators one at a time (separate models) except as noted.
[2]At TSP = 100 $\mu g/m^3$, SO_4 = 15 $\mu g/m^3$, corrected for migration.
[3]NS = not statistically significant, confidence limits not available.

At this point in the development of the methodology for population-based cross-sectional studies (which was discussed in the 1982 CD and the 1986 Addendum [U.S. Environmental Protection Agency, 1982a, 1986a]), it appeared that the findings of national cross-sectional analyses (Table 12-14) showed that including additional socioeconomic variables in the model reduced the apparent effects of sulfate for the 1970 time period. However, the 1974 study found even larger effects of sulfate, but it could not be ascertained whether this was due to the regression model used or to the particular data set considered.

Kim (1985) analyzed total mortality data for 1970 in a cross-sectional analysis of 49 U.S. cities. Pollutants considered were TSP and the benzene-soluble organic fraction of TSP (BSO), in 5 different formats: averaged over the single years 1968, 1969, and 1970; averaged for 1969 to 1970, and for 1968 to 1970. This analysis was intended to test for lagged effects, but one might also expect the multiple-year averages to be superior because of the reduction of random sampling errors. Kim's lag analysis was largely inconclusive. He concluded "the effects of total mortality in 1970 may be due to the air pollution in 1969, although it is not possible to pinpoint a lag-effect between the time of exposure to air pollution and the time of death."

More recently conducted cross-sectional and/or prospective cohort studies address many of the concerns noted for the above-reviewed older studies.

Studies of 1980 SMSA Mortality

Ozkaynak and Thurston (1987) analyzed 1980 total mortality in 98 SMSAs, using data on PM_{15} and $PM_{2.5}$ from the EPA inhalable particle (IP) monitoring network for 38 of these locations. The sulfate data from this network were not used in this study. The independent variables used are given in Table 12-15 (first two studies); in general, the regression modeling approach was similar to that of Lave and Seskin (1970). The results presented in Table 12-15 are from their "basic" regression model. Additional variables were explored, including spatial correlation variables intended to examine regionality and latitude and longitude variables. The sulfate measurements that Ozkaynak and Thurston used may have been affected by artifacts from the high-volume sampler filters (Lipfert, 1994b); this is also suggested by the fact that their mean SO_4^{2-} value exceeds those of previous years and the mean from the IP data set (compare studies 1 and 9 in Table 12-15).

Ozkaynak and Thurston (1987) ranked the importance of the various pollutants mainly by relative statistical significance in separate regressions. They concluded that the results were "suggestive" of an effect of particles on mortality decreasing with particle size, although in the basic model only SO_4^{2-} was significant. In some of the other models, $PM_{2.5}$ was also significant and PM_{15} nearly so. However, if the effects are judged by elasticities rather than significance levels, SO_4^{2-}, $PM_{2.5}$, and PM_{15} would be judged as equivalent, with TSP ranking somewhat lower. The indicated effect of SO_4^{2-} would be reduced from an elasticity of 0.086 to about 0.05 by accounting for filter artifacts (Lipfert, 1994b). Ozkaynak and Thurston (1987) also used source apportionment techniques to estimate that particles from coal combustion and from the metals industry appeared to be the most important.

The coefficients and significance levels obtained for TSP by Ozkaynak and Thurston (1987) may be the result of the TSP data they used, which were based on a single monitoring station in each SMSA and thus are unlikely to be fully representative of population exposures. For example, it is possible that the relatively poor showings of TSP and PM_{15} in their models resulted from the additional measurement error rather than from a difference in underlying toxicity. Ozkaynak and Thurston also noted the need for more elaborate model specifications, larger data bases, and more complete sets of predictor variables, including migration, smoking, and more detailed specification of race and ethnicity. This study did not specifically address the question of lagged pollution variables.

The analysis by Lipfert et al. (1988) comprised a statistical analysis of spatial patterns of 1980 U.S. central city total mortality (all causes), evaluating demographic, socioeconomic, and air pollution factors as predictors (studies 3 to 5 in Table 12-15). The advantages of studying central cities versus SMSAs include potentially better measures of exposure because of the smaller areas, and sufficient numbers of observations to allow analysis of subsets of locations. In this study, sulfate and iron particles were significant (joint) predictors of all-cause mortality in about 180 cities. If the elasticities for SO_4^{2-} were corrected to account for the filter artifacts, they would be reduced by about 50% in this study (i.e., to about 0.01 to 0.05). The data on PM_{15} and $PM_{2.5}$ were only available for 68 cities; neither pollutant was significant in this data set but their elasticities were in the same range found for other pollutants (0.013 to 0.05). This study also allowed a test of lagged pollution data as a means of attempting to distinguish acute from chronic

responses; using 1970 TSP and SO_4^{2-} data to predict 1980 city mortality was slightly less effective than using ca. 1980 data for these pollutants as predictors.

Data from up to 149 metropolitan areas (mostly SMSAs) were analyzed in a study of the relationships between community air pollution and "excess" mortality due to various causes for the year 1980 (Lipfert, 1993). Several socioeconomic models, including the model proposed by Ozkaynak and Thurston (1987), were used in cross- sectional multiple regression analyses to account for non- pollution variable effects (see variables listed for studies 6 to 11 in Table 12-15). Cause-of-death categories analyzed include all causes, nonexternal causes (ICD9 0-800), major cardiovascular diseases (ICD9 390-448), and chronic obstructive pulmonary diseases (COPD) (ICD9 490-96). The patterns for the first three groupings were quite similar but differed markedly from the patterns of COPD mortality, which tend to be higher in the Western United States. Regressions were performed for these cause-of-death groupings as annual mortality rates ("linear" models) and as their logarithms ("log-linear" models). The original regressions used base-10 logarithms; the results have been converted to natural logarithms for this review. Two different sources of measured air quality data were utilized: data from the U.S. EPA AIRS database (TSP, $SO_4^=$, Mn, and O_3 from a long-term average isopleth map) and data from the inhalable particulate (PM_{15}) network; the latter data (PM_{15},$PM_{2.5}$ and $SO_4^=$ from the IP filters) were only available for 63 locations. All PM data were averaged across all the monitoring stations available for each SMSA; the TSP data were restricted to the year 1980 and were based on an average of about 10 sites per SMSA.

The associations between mortality and air pollution were found to be dependent on the socioeconomic factors included in the models, the specific locations included in the data set, and the type of statistical model used, as was the case with 1970 data (Lipfert, 1984). In the expanded analysis, stepwise regressions were run for each mortality variable and a "parsimonious" model was developed that had statistically significant coefficients for the non-pollution variables. Most of these coefficients also agreed with exogenous estimates of the "correct" magnitudes. Using these models, statistically significant associations were found between TSP and mortality due to non-external causes with the log-linear models evaluated, but not with a linear model. Sulfates, manganese, inhalable particles (PM_{15}), and fine particles ($PM_{2.5}$) were not significantly ($P < 0.05$) associated with mortality with any of the parsimonious models, although $PM_{2.5}$ and Mn

were nearly significant in the linear models (p=0.07) and significance may have been affected by the use of smaller data sets. This study showed that $PM_{2.5}$ was the "strongest" particulate variable with linear models, but that TSP performed better in log-linear models. Scatter plots and quintile analyses suggested that a TSP threshold might be present for nonexternal causes and for COPD mortality at around 65 $\mu g/m^3$ (annual average).

This study supported the previous findings of associations between TSP and premature mortality and also the hypothesis that improving the accuracy of pollutant exposure data tends to increase statistical significance. Similarly, the lack of significance for $SO_4^=$ may be partly relate to flawed measurement methods used at the time. The ambiguity between linear and log-linear models probably reflects the effects of influential observations.

Population-Based Mortality Studies by Age and Cause of Death

Only a few of the many published ecological mortality studies analyzed subgroups by age and cause. Lave and Seskin (1977) used very broad age groups (0 to 14, 15 to 44, 45 to 64, 65+) with 1960 and 1969 data, which limited the usefulness of the analysis because of the failure to account for age differences within these groupings. Lave and Seskin also examined a large number of disease-specific mortality rates using 1960 and 1961 data. Cancers and cardiovascular diseases were associated with the flawed "minimum" sulfate variable, but respiratory causes tended to be associated with TSP. Lipfert (1978) considered for U.S. cities, 1969 to 1971, infant mortality, ages 1 to 44, and from 45 to 85 by 10-year groups. Very little significance was found below age 65; for ages 75+, SO_4^{2-}, TSP, Fe and Mn were significant (one at a time). Lipfert (1978) considered nonexternal causes, total cancers, respiratory cancer, respiratory disease (asthma, bronchitis, emphysema) and all other diseases (mainly cardiovascular). Only Fe was significantly associated with total cancers, only Mn with respiratory cancer, Fe was positively associated with respiratory diseases but SO_4^{2-} was strongly <u>negatively</u> associated with respiratory disease mortality. Lipfert (1993) found that PM was not significantly associated with mortality from major cardiovascular causes for 1980 SMSA mortality, which implies that other causes of death must be involved for this pollutant. Note that between 1960 and 1980 there were major improvements in cardiovascular mortality, resulting in some changes in the geographic patterns. For 1980 SMSA mortality, COPD mortality was strongly associated with TSP with a variety of

regression models. Significant associations were found between TSP and COPD mortality for both linear and log-linear models (study 11 in Table 12-15). When the sulfate contribution to TSP was subtracted, the relationship with COPD mortality was slightly strengthened but no comparable analyses were carried out for coarse respirable particles or for non-sulfate component of fine particles or respirable particles. $PM_{2.5}$ was a significant predictor of heart disease mortality only when the regression model was restricted to the variables used by Ozkaynak and Thurston (1987).

Cross-Sectional Infant Mortality Studies

Bobak and Leon (1992) studied neonatal mortality (ages less than 1 month) and post-neonatal mortality (ages 1 to 12 months) from 1986 to 88 in 46 administrative districts in the Czech Republic, in relation to annual averages of PM_{10}, SO_2, and NO_2. The observations comprised 121 combinations of districts and years, ranked into quintiles by mean pollution level for analysis (5 districts had insufficient data). The analysis was ecological in design, in that the outcome variable was the death rate per 1,000 live births and district-wide averages were used as the control variables (mean income, mean savings, mean number of persons per car, proportions of total births outside of marriage, and the rate of legal abortions. In the United States, for example, infant mortality is a strong function of income or poverty status, reflecting the effects of access to pre- and post-natal medical care.

The mean pollutant values were 68.5, 31.9, and 35.1 $\mu g/m^3$ for PM_{10}, SO_2, and NO_2, respectively. This study appears to be based on a denser air monitoring network than many of its predecessors in the U.S.; the mean population per monitor was only about 50,000 and many ecological studies in the U.S. are based on values an order of magnitude higher than this. Two of the three pollutants were highly correlated ($R = 0.80$ for SO_2 versus NO_2), indicating a common source (combustion). Correlations with PM_{10} were lower (0.15 and 0.26), reflecting the fact that the particle sources were more diverse and included such sources as cement production plants in some districts. The maps presented in the paper suggested little likelihood for spatial autocorrelation, although this topic was not discussed directly. Bobak and Leon (1992) addressed the pollutant collinearity problem by presenting results for each pollutant alone and for

the combination of all three. Results were also presented for analyses with and without socioeconomic adjustments.

The statistics used to indicate significant associations were chi-square p-values for trend across the 5 quintiles, with the relative risks set to 1.0 for the lowest quintiles. Highly significant trends ($p < 0.01$) were seen after socioeconomic adjustment for postneonatal mortality only with PM_{10}, even after including the other pollutants. Post-neonatal respiratory mortality showed highly significant trends for all 3 pollutants, but only PM_{10} retained significance ($p=0.013$) with all 3 pollutants. Because of the use of multiple years of data for 41 common locations and the strong likelihood of temporal persistence in annual average air quality, the true number of degrees of freedom may be 41 rather than 121. For this reason, a higher standard of association should be applied to these results ($p < 0.01$ rather than $p < 0.05$). Although Bobak and Leon (1992) elected to analyze their data in terms of linear responses over the entire pollutant range, their results were suggestive of a threshold at the third quintile or higher (mean $PM_{10} = 67\ \mu g/m^3$).

It is not clear from the design of this study whether the reported effects are acute or chronic. Pollution values were averaged over the same years used to aggregate deaths; thus it is possible that exposure did not precede death in all cases. In any event, it may be difficult to distinguish delayed acute from chronic responses for lifetimes as short as a few months. Among the previous U.S. studies reviewed, Lave and Seskin (1977) found infant mortality to be associated with TSP; Lipfert (1978) found marginal significance for the Fe and Mn portions of TSP and a negative association with SO_4^{2-}(ca. 1970).

Summary of Population-Based Cross-Sectional Mortality Studies

Although most of these studies covered the entire U.S. using the basic paradigm of Lave and Seskin (1970), there are major differences in the degree of confounder control, including the air pollutants investigated. Most of the studies found pollutant elasticities (i.e., mean effects) of 0.02 to 0.08, although the associations with air pollution and specific causes of death varied. However, all of these studies found at least some association between air pollution and mortality on an annual average basis. There was a slight suggestion that elasticities may be decreasing over time (1960 to 1980). It was not possible to determine whether the mortality associations were stronger for pollution measured the same year or in previous years. Analyses by age and cause of

death were limited; the most consistent associations were for the elderly, especially ages 75+, and for respiratory disease mortality and TSP.

Pollutant thresholds were considered by some authors, with mixed success. Studies of 1970 and 1980 SMSA mortality found suggestions of a TSP threshold in the range 60 to 85 $\mu g/m^3$, but perhaps the strongest evidence of a threshold was found for 1980 sulfate, at around 10 $\mu g/m^3$. However, the strong effects that errors in estimated exposures can have on obscuring the true shape of a dose-response function must be considered when evaluating observational evidence for thresholds (see Section 12.2.5).

12.4.1.3 Prospective Mortality Studies

Studies considered here utilized data on the relative survival rates of individuals, as affected by age, sex, race, smoking habits, and certain other individual risk factors. This type of analysis has a substantial advantage over the population-based studies, because the identification of the actual decedents allows stratification according to important individual risk factors such as smoking. Such stratification allows tests of the hypothesis that certain segments of the population may be more sensitive to air pollution than others, which is a major shortcoming of population-based studies. In addition, having data on the actual personal characteristics of each decedent, such as their education or body mass, as opposed to community classification data such as "percent overweight", allows for the possibility of a detailed (i.e., nonlinear) specification of risk factors that is clearly more difficult to assess in a population-based study. However, analyzing individuals also entails dealing with increased variability in outcome and thus requires large sample sizes if effects as small as those typically found in population studies are to be detected with significance. Since none of the prospective cohort studies had data on personal exposures to air pollution, this precludes analysis within cities or by type of exposure (primarily indoor versus outdoor, or coincident versus accumulated, for example). In this limited sense, these studies are also "ecological."

The newer prospective studies (Abbey et al., 1991a; Dockery et al., 1993; and Pope et al., 1995b) are reviewed here. Two older studies, by Morris et al. (1976) and by Kryzanowski and Wojtyniak (1982) are also examples of prospective studies, but without information on respirable

particles, and thus are not discussed. The main findings from the three most recent studies are summarized in Table 12-16.

California Seventh-Day Adventists

Abbey et al. (1991a) described a prospective study of about 6,000 white, non-Hispanic, nonsmoking, long-term California residents who were followed for 6 to 10 years, beginning in 1976. The study was designed to test the use of cumulative exposure data as an explanatory factor for disease incidence and chronic effects. Ambient air quality data dating back to 1966 were used, and the study was restricted to those who lived within 5 miles of their current residence for at least 10 years. All of the air quality monitors in the state were used to create individual exposure profiles (duration of exposure to specific minimum concentration levels) for each participant, by interpolating to their zip code centroids based on the 3 nearest monitoring stations. Pollutant species were limited to TSP and O_3 in this paper; oxidant concentrations were used in the early part of the monitoring record. Health endpoints evaluated and the numbers of cases included: newly diagnosed cancers (incidence at any site) for males, 115; any cancer site for females, 175; respiratory cancer, 17; definite myocardial infarction, 62; mortality from any external cause, 845; and respiratory symptoms, 272. The Cox proportional hazards model was used, considering age, sex, past smoking, education, and presence of definite symptoms of asthma, chronic bronchitis, or emphysema of airway obstructive disease (AOD) in 1977 as individual risk factors, together with various exposure indices for TSP or O_3 (considered separately). Data on occupational exposures and history of high blood pressure were available but were not used in the mortality model. No data were available on climate, body mass, income, migration, physical activity levels or diet. Separate results by gender were not reported for nonexternal mortality.

TABLE 12-16. PROSPECTIVE COHORT MORTALITY STUDIES

Source	Health Outcome	Population	Time Period/ No. Units	PM Indicators	PM Mean ($\mu g/m^3$)	PM Range/ (Std. Dev.)	Sites Per City	Total Deaths	Model Type	PM Lag Structure	Other Pollutants	Other Factors	Relative Risk[1] at SO_4 = 15, PM_{15} = 50, $PM_{2.5}$ = 25	RR. Confidence Interval	Elasticity
Abbey et al. (1991a)	Total mortality from disease	Calif. 7th Day Adventist	1977-82 Defined by air monitoring sites	24 h TSP > 200	102	25-175 (annual avg)	NA	845	Cox proportional hazards	10 yrs	none	age, sex, race, smoking, education, airway disease	0.99 TSP[1]	(0.87-1.13)[1]	NS[2]
Dockery et al. (1993)	Total mortality	White adult volunteers in 6 U.S. cities[3]	1974-91	PM $PM_{2.5}$ SO_4	29.9 18 7.6	18-47 11-30 5-13	1	1429	Cox proportional hazards	none	none	age, sex, smoking, education, body mass, occup. exposure hypertension[4], diabetes[4]	1.42 PM_{15} 1.31 $PM_{2.5}$ 1.46 SO_4	(1.16-2.01) (1.11-1.68) (1.16-2.16)	0.25 0.22 0.23
Pope et al. (1995b)	Total mortality	American Cancer Society, adult volunteers in U.S.	1982-89 $PM_{2.5}$ 50 cities SO_4 151 cities	$PM_{2.5}$ SO_4	18.2 11[5]	9-34 4-24	1 1	20,765 38,963	Cox proportional hazard	none	none	age, sex, race, smoking, education, body mass, occup. exposure, alcohol consumption, passive smoking, climate	1.17 $PM_{2.5}$ 1.10 SO_4	(1.09-1.26) (1.06-1.16)	0.117 0.077

[1]For 1,000 h/yr > 200 $\mu g/m^3$.
[2]NS = non significant, confidence limits not shown.
[3]Portage, WI; Topeka, KS; Watertown, MA; Harrisman-Kingston, TN; St. Louis, MO; Steubenville, OH.
[4]Used in other regression analyses not shown in this table.
[5]Value may be affected by filter artifacts.

Of these endpoints, respiratory symptoms and female cancers (any site) were associated with TSP exposure. Neither heart attacks or nonexternal mortality was associated with either pollutant. The authors felt that possible errors in their estimated exposures to air pollution may have contributed to the lack of significant findings, and a later version of the data base include estimates of attenuation resulting from time spent indoors (Abbey et al., 1993), but mortality was not considered in the 1993 paper.

The follow-up analysis (Abbey et al., 1995b) considered exposures to $SO_4^{2-,}$ PM_{10} (estimated from site-specific regressions on TSP), $PM_{2.5}$ (estimated from visibility), and visibility per se (extinction coefficient). No significant associations with nonexternal mortality were reported, and only high levels of TSP or PM_{10} were associated with AOD or bronchitis symptoms.

This study used an unique air quality data base which was developed for the express purpose of studying the effects of long-term cumulative exposures to community air pollution (Abbey et al., 1991b). The technique was shown to provide reliable spatial interpolations that were somewhat better for O_3 than for TSP, in keeping with expectations based on the regional nature of O_3. TSP may have been an inadequate index of exposure to inhalable particles, especially in this relatively arid region where one might expect to find a large fraction of non-inhalable particles. However, no attention was given to temporal matching of air quality and health; the studies using this data base were intended to evaluate the hypothesis that health is affected by cumulative long-term pollution exposure at some undetermined time, as opposed to acute or coincident exposures. Note that the data base began in 1966 and the mortality follow-up began 10 years later. Because air quality generally improved during this period, the highest concentrations are likely to have occurred in the earlier part of the record, and thus one would not expect spatially-based correlations to also reflect the sum of acute effects, as would be the case when air quality and health data are also matched in time. Note that the range of air quality levels experienced in California from 1966 onward is at least as large as that currently experienced in the rest of the United States, including the nation's highest O_3 levels, annual average TSP up to about 175 $\mu g/m^3$, and annual average SO_4^{2-} up to about 9-11 $\mu g/m^3$ (Lipfert, 1978). Thus, lack of adequate range in the pollution variables does not appear to be a valid reason for the lack of statistical significance. However, levels of SO_2 and of certain trace metals such as Mn tend to be

lower in California than in the midwestern parts of the United States with larger concentrations of heavy industry.

The finding of Abbey et al. (1991a) of no association between long-term cumulative exposure to TSP or O_3 and all natural-cause mortality may be interpreted as showing the absence of chronic responses after 10 years but not necessarily the absence of (integrated) acute responses, since coincident air pollution exposures or integrated exposures over the preceeding few years were not considered. It is also possible that the latency period for chronic effects may exceed 10 years and that additional follow-up might still reveal chronic effects. The magnitudes of the other risk factors considered were not given by Abbey et al. (1991a), which precludes comparison with the other studies.

Prospective Cohort Study in Six U.S. Cities

Dockery et al. (1993) analyzed survival probabilities among 8,111 adults who were first recruited in the mid-1970s in six cities in the eastern portion of the United States. The cities are: Portage, WI, a small town north of Madison; Topeka, KS; a geographically-defined section of St. Louis, MO; Steubenville, OH, an industrial community near the West Virginia-Pennsylvania border; Watertown, MA, a western suburb of Boston; and Kingston-Harriman, TN, two small towns southwest of Knoxville. This selection of locations thus comprises a transect across the Northeastern and Northcentral United States, from suburban Boston, through Appalachia, and into the upper Midwest.

The adults were white and aged 25 to 74 at enrollment. In each community, about 2,500 adults were selected randomly, but the final cohorts numbered 1,400 to 1,800 persons in each city (Ferris et al., 1979). Follow-up periods ranged from 14 to 16 years, during which from 13 to 22% of the enrollees died. Of the 1,430 death certificates, 98% were located, including those for persons who had moved away and died elsewhere. However, no information was given in the paper about the actual locations of death. The bulk of the analysis was based on all-cause mortality; no mention was made of subtracting external causes.

These cohorts have been studied extensively for respiratory health (Dockery et al., 1985). Air monitoring data were obtained from routine sampling stations and from special instruments set up by the research team. Individual characteristics of the members (and thus of the decedents)

considered included smoking habits, an index of occupational exposure, body mass index, and completion of a high school education. The Cox proportional hazards model was used to estimate coefficients for the individual risk factors after stratifying by gender and age (5-year groups). The effects of air pollution were evaluated in two ways: by evaluating the relative risks of residence in each city relative to Portage (the city with the lowest pollution levels for most indices), and by including the community-average air quality levels directly in the models. Since only six different long-term average values were available for each pollutant, the effective degrees of freedom are greatly reduced by this procedure.

Most of the air quality measures were averaged over the period of study, in an effort to study long-term (chronic) responses; the specific averaging periods varied by pollutant. Steubenville, Kingston-Harriman, and St. Louis were the most polluted cities and also had the oldest and least educated cohorts and the heaviest rates of smoking among the six cities.

The index of smoking rate used in this study was pack-years, defined as the average number of packs of cigarettes smoked per day times the number of years of smoking. This metric is also a function of age. Current and former smokers were treated separately. This smoking metric assumes that health impacts are defined by cumulative tobacco use rather than by current rate of consumption. The risk per pack-year was higher for former smokers (0.015 per pack year) compared to current smokers (0.01 per pack year); and the finding of a risk per pack year for current smokers that increased with consumption rate suggests that the current rate of smoking may also have merit as a health impact index (especially if the age of starting smoking varies). The total effect of smoking was thus defined as the relative risk of being a smoker plus the risk associated the number of pack-years in question.

The index of socioeconomic status used was having less than a high school education; Rogot et al. (1992a) show that this index is a good measure of mortality differences due to differences in education for white men but not for white women. For women, relative mortality risk continues to increase for educational attainments less than completion of high school. The index of occupational exposure to air pollution (dusts or fumes) did not take into account the length or degree of exposure or the nature of the agents involved. Occupational exposure to dusts or fumes was not found to be a significant risk factor; this outcome may have resulted from

the lack of specificity of the index used. The average percentages having occupational exposure were high, ranging from 28 to 53%, with an average across all cities of 45%.

The index of physiology used was the body mass index (BMI), defined as weight divided by height squared (kg/m^2), treated as a linear relationship. The relative risk of increased body mass was similar to that found by Sandvik et al. (1993), where it was not statistically significant, but other investigators have found that the relationship is U-shaped rather than linear and may interact with other risk factors, especially smoking (Grønbæk et al., 1994). Mispecification of a confounder may result in inflation of the effect being evaluated (Klepper et al., 1993) although attenuation of effect sizes is the more typical effect of measurement error.

No consideration was given to possible independent effects of occupation classification, other personal lifestyle variables such as diet or physical activity, migration, or income. Presumably, each subject was characterized by his status at entry to the study; follow-up data on possible changes in risk factors over time were not mentioned. Since the air quality data used in this study were largely obtained from "private" monitoring rather than from public archives, comparisons of the average levels with routine monitoring data were of some interest. No serious disagreements were found, except that it might have been preferable to consider peak rather than average levels of ozone, as has been done in most of the studies of acute effects of ozone on mortality. However, the size-classified particulate data began in 1980 while TSP data began in 1974; from 1974 to 1980 there were large reductions in TSP (and probably in the size-classified particles as well), so that it appears that the size-classified data are less representative of cumulative exposures than TSP. Sulfate appeared to be intermediate in this regard. In this sense, there is a mismatch in time between the air quality data, which were obtained after the study began, and the descriptive data on individuals, which pertain to the period before entry into the study.

A more complete breakdown of relative risk estimates by city, sex, smoking status, education, and body mass index is given in Table 12-17. The mean $PM_{2.5}$ values are provided for reference, but the adjusted relative risks used only age, smoking, education, and body mass as covariates. The RR values for men and women combined are plotted in Figure 12-8 for each pollutant. It should be noted that the apparently linear relationship between fine particles and risk

is less linear if plotted separately for men and for women, but the confidence intervals then become much wider due to smaller samples.

TABLE 12-17. RELATIVE MORTALITY RISKS IN SIX CITIES

			Adjusted Risks		
Risk Factor	$PM_{2.5}$ Data ($\mu g/m^3$)	Crude Risk	All[2]	Men[2]	Women[2]
Residence					
Portage	11.0 (1980-7)[3]	1.0[1]	1.0	1.0	1.0
Topeka	12.5 (1980-8)	0.90	1.01	1.04	0.97
Watertown	14.9 (1980-5)	1.16	1.07	0.94	1.22
Harriman	20.8 (1980-7)	1.16	1.17	1.21	1.07
St. Louis	19.0 (1980-6)	1.48	1.14	1.15	1.13
Steubenville	29.6 (1980-7)	1.51	1.26	1.29	1.23
Smoking Status					
Current			1.59	1.75	1.54
Previous			1.20	1.25	1.18
No high school education			1.19	1.22	1.13
Body mass index of 4.5			1.08	1.03	1.11

[1]Baseline annual crude death rate = 10.73 per thousand population
[2]Adjusted for age, smoking, education, and body mass
[3]Period of $PM_{2.5}$ air monitoring

Source: Dockery et al. (1993)

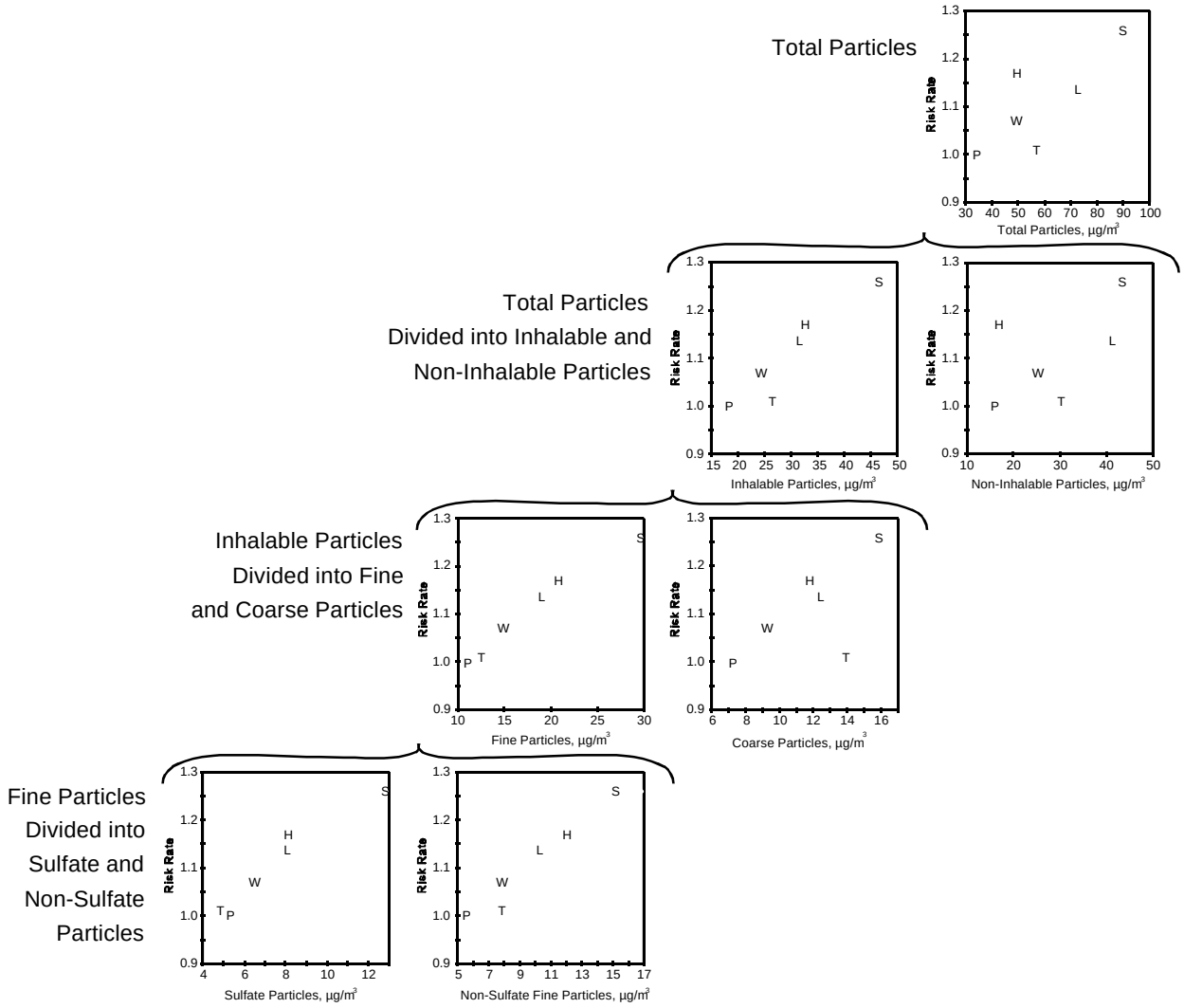

Figure 12-8. Adjusted relative risks for mortality are plotted against each of seven long-term average particle indices in the Six City Study, from largest range (total suspended particles, upper right) through sulfate and nonsulfate fine particle concentrations (lower left). Note that a relatively strong linear relationship is seen for fine particles, and for its sulfate and non-sulfate components. Topeka, which has a substantial coarse particle component of inhalable (thoracic) particle mass, stands apart from the linear relationship between relative risk and inhalable particle concentration.

Source: U.S. EPA replotting of results from Dockery et al. (1993).

Based on statewide mortality data, substantial differences in survival rates would be expected across this transect of the Northeastern U.S. and were observed (Table 12-17). The long-term average mortality rate in Steubenville was 16.2 deaths per 1,000 person-years; in Topeka, it was 9.7, yielding a range in average (crude) relative risk of 67% among the six cities. After individual adjustment for age, smoking status, education, and body-mass index, the range in average relative risk was reduced to 26%. The relative importance of the adjustments for age, smoking, education, and body mass in determining the final ranks of the cities may be seen from the table. Also, there is more scatter for men and women separately than when combined, presumably because of the reduction in sample size.

Dockery et al. (1993) report that "mortality was more strongly associated with the levels of fine, inhalable, and sulfate particles" than with the other pollutants, which they attributed primarily to factors of particle size. They provided relative risk estimates and confidence limits based on the differences between air quality in Steubenville and in Portage for these three pollutants. However, it is relatively simple to independently estimate these coefficients from the adjusted risks and pollutants levels in each of the six communities. These estimates correspond quite closely to the figures given by Dockery et al. based on output from the Cox proportional hazards model. However, because there are only 6 different values for the air quality data, the resulting confidence limits are considerably wider than those for the risk factors having individual data. These estimates are given in Table 12-18, as a means of comparing the various pollutants and combination of pollutants. As in the original paper, the relative risks are based on the difference in air pollution between Steubenville and Portage. The data for 1970 TSP (corresponding to a lag of about 12 years) were obtained from Lipfert (1978), assuming that Madison could represent Portage, WI, as was done in the analysis of Schwartz et al. (1996b).

Table 12-18 shows only small differences among many pollutants, including SO_2 and NO_2, owing in part to the strong collinearity present. Note that TSP and the coarse particle variables created by subtracting PM_{15} from TSP and $PM_{2.5}$ from PM_{15} were not significant, suggesting that particles larger than about 15 μm in aerodynamic diameter may be less important; this outcome may reflect in part greater spatial variability within the communities for these measures. The non sulfate portion of $PM_{2.5}$ had the tightest confidence limits

TABLE 12-18. ESTIMATED RELATIVE RISKS OF MORTALITY IN SIX U.S. CITIES ASSOCIATED WITH A RANGE OF AIR POLLUTANTS

Species	Regr. Coeff.	Standard Error	Range	Rel. Risk	95% CIs (n=6)
PM_{15}	0.0085	(0.0026)	28.3	1.27	(1.04-1.56)
$PM_{2.5}$	0.0127	(0.0034)	18.6	1.27	(1.06-1.51)
SO_4^{2-}	0.0297	(0.0081)	8.5	1.29	(1.06-1.56)
TSP	0.0037	(0.0014)	55.8	1.22	(0.99-1.53)
TSP-PM_{15}	0.0042	(0.0032)	27.5	1.12	(0.88-1.43)
PM_{15}-$PM_{2.5}$	0.0178	(0.0098)	9.7	1.19	(0.91-1.55)
$PM_{2.5}$-SO_4	0.0255	(0.0029)	8.4	1.24	(1.16-1.32)
PM_{15}-SO_4	0.0121	(0.0034)	18.1	1.24	(1.05-1.48)
SO_2	0.0093	(0.0032)	19.8	1.20	(1.01-1.43)
NO_2	0.0126	(0.0046)	15.8	1.22	(1.00-1.49)
1970 TSP	0.0014	(0.00044)	154.0	1.25	(1.03-1.50)

Source: U.S. EPA recalculations based on results of Dockery et al. (1993).

(SO_4^{2-} was multiplied by 1.2 before subtraction, assuming an average composition of NH_4HSO_4). Note also that the estimated 1970 TSP variable performed slightly better than the TSP data used by Dockery et al. (ca. 1982) thus suggesting a role for previous pollution exposure. However, all of the differences in relative risks and their confidence limits could have occurred due to chance, given the availability of only 6 observations. Dockery et al. noted that the mean ozone level varied little among cities. This might not have been the case if some measure of peak concentration had been used instead of the overall mean (24-h averages). No relationship was found for aerosol acidity (H^+), but only limited data were available. The effects of both sulfate and non-sulfate fine particles seems rather similar, as shown in Figure 12-8. It seems plausible that there may be PM effects related to particle size that are independent of sulfate content or acidity of the particles.

In comparing the most and least polluted cities, Dockery et al. also report elevated risks for cardiopulmonary causes (1.37, [1.11 to 1.68]) and lung cancer (1.37, [0.81 to 2.31], not significant). The relative risk for all other causes of death was 1.01 (0.79 to 1.30). When the six cities were considered individually, only Steubenville showed a statistically significant ($p < 0.05$) elevated risk with respect to the least polluted city (Portage).

Comparison of the pollution risks among the various cohort subsets considered is one of the most important outcomes of a study on individuals. Such comparisons must account for the higher variability among subgroups, however, and the study was not capable of distinguishing excess risks between subgroups less than about 18% (i.e., an excess risk of 1.18 cannot be distinguished from one of 1.36, for example). Although none of these subgroup differences were statistically significant, the mortality risks associated with area of residence (and thus air pollution) were higher for females and for smokers and the risks were also higher for those occupationally exposed compared to the nonexposed. Because of reduced uncertainties about their exposure to air pollution not reflected in the outdoor monitoring data used in this study, it is possible that the relative risk estimates for nonsmokers and the nonoccupationally exposed might be the most reliable estimates (1.19 and 1.17, respectively). See Chapter 7 for a discussion of exposure measurement errors.

In correspondence, Moolgavkar (1994) raised issues of residual confounding, age adjustment and smoking controls. In their response, Dockery and Pope (1994a) agreed that confounding is a potential concern but did not address the possibility that variables other than the ones they considered might be important. They dealt with the age adjustment issue quantitatively and pointed out that the air pollution risk estimates were reasonably stable over different subgroups by smoking status. Age is a potentially important covariate because it measures both susceptibility to health effects and cumulative exposure to pollutants. There is also a possible interaction involving age, air pollution, and time of death, since air pollution concentrations in some communities such as Steubenville and St. Louis decreased substantially during the years preceding and during the period of the study. No use was made of time- and age-dependent cumulative exposure indices in this study.

The authors of this study appear to have made the most of the available individual data on some of the most important mortality risk factors. They were quite cautious in their conclusions,

stating only that the results suggest that fine-particulate air pollution "contributes to excess mortality in certain U.S. cities." There are several other important outcomes:

- None of the population subgroups examined appeared to be significantly more sensitive to air pollution than any other. Since the relative risks were virtually unchanged by excluding subjects with hypertension and diabetes, this finding might also be extended to those with pre- existing chronic diseases. This apparent homogeneity of response has implications regarding the acceptability of population-based studies in which such stratification is not possible.

- The implied regression coefficients are much larger (about an order of magnitude) than those found in either type of cross-sectional study. This could be interpreted as evidence that the population-based studies underestimate the effects, that the chronic effects of air pollution on mortality far exceed the acute effects, or that not all of the spatial confounding has been controlled. Use of linear models for non-linear effects (body-mass index) and failure to control for alcohol consumption, diet, exercise and migration may have contributed to the relatively large effects indicated for air pollution (Lipfert and Wyzga, 1995a).

- If the responses to air pollution truly are chronic in nature, it is logical to expect that cumulative exposure would be the preferred metric (Abbey et al., 1991a). Pollution levels 10 years before this study began were much higher in Steubenville and St. Louis, as indexed by TSP from routine monitoring networks. Estimates of previous levels of fine particles are more difficult, but atmospheric visibility data suggest that previous levels may have been higher in winter, but not necessarily in summer. These uncertainties make it difficult to accept quantitative regression results based solely on coincident monitoring data. For example, annual average TSP in 1965 in Steubenville was about three times the value used by Dockery et al.; use of the older data would have reduced the implied regression coefficients and the relative risks, but not the elasticities. On the other hand, if the responses reflect primarily the last few years of integrated exposure then the concurrent average monitoring data would be reasonably predictive.

Because it seems unlikely that any of the perceived shortcomings of this study could have resulted in bias sufficient to reduce the risk estimates to levels less than those found in acute mortality studies, the study of Dockery et al. (1993) appears to provide support for the hypothesis that the results of long-term air pollution studies must also reflect the presence of acute effects on mortality as integrated over the long term, as suggested by Evans et al. (1984a). It may also be concluded that support has been shown for the existence of chronic effects; these two possibilities are not mutually exclusive. However, these conclusions must be qualified by the realization that

not all of the relevant socioeconomic factors may have been properly controlled in this study. Some quantitative estimates of these effects are given below.

American Cancer Society Study

Pope et al. (1995b) analyzed 7-year survival data (1982 to 1989) for about 550,000 adult volunteers obtained by the American Cancer Society (ACS). The Cox proportional hazards model was used to define individual risk factors for age, sex, race, smoking (including passive smoke exposure), occupational exposure, alcohol consumption, education, and body-mass index. The deaths, about 39,000 in all, were assigned to geographic locations using the 3-digit zip codes listed at enrollment into the ACS study in 1982. Relative risks were then computed for 151 metropolitan areas defined by these zip codes and were compared to the corresponding air quality data, ca. 1980. The sources of air quality data used were the EPA AIRS system for sulfates, as obtained from high-volume sampler filters for 1980, and the Inhalable Particulate Network for fine particles ($PM_{2.5}$). The latter data were obtained from dichotomous samplers during 1979-81; Pope et al. used the values from this data base reported by Lipfert et al., 1988 (this study is discussed above), but only 50 $PM_{2.5}$ locations could be matched with the death data. The correlation between the two pollutants was 0.73. The sulfate values from the inhalable particle filters, which are thought to be free from artifacts, were not used in this study. Causes of death considered included all causes, cardiopulmonary causes (ICD-9 401-440, 460-519), lung cancer (ICD-9 162), and all other causes.

This study took great care with the potential confounding factors for which data were available. Several different measures of active smoking were considered, as was the time exposed to passive smoke. The occupational exposure variable was specific to (any of) asbestos, chemicals/solvents, coal or stone dusts, coal tar/pitch/asphalt, diesel exhaust, or formaldehyde. The education variable was an indicator for having less than a high-school education. However, alcohol use and body-mass index were considered as linear predictors of survival, whereas other studies have indicated these effects to be non-linear (U or J-shaped) (Doll et al., 1994; Grønbæket al., 1994). Pope et al. (1995b) did not report the relative risk coefficients they obtained for these cofactors, which does not allow comparison of findings for the non- pollution variables with exogenous estimates from independent studies.

Risk factors not considered by Pope et al. (1995b) include income, employment status, dietary factors, drinking water hardness and physical activity levels, all of which have been shown to affect longevity (Sorlie and Rogot, 1990; Belloc, 1973; Pocock et al., 1980). In addition, they did not discuss the possible influences of other air pollutants. For example, Lipfert et al. (1988) found that it was not possible to separate the effects of SO_2, SO_4^{2-}, and NO_x from one another, and Lipfert (1992) found some evidence for the effects of ozone in cross-sectional mortality regressions for U.S. metropolitan areas in addition to associations between TSP and all-disease and COPD mortality.

The ACS cohort is not a random sample of the U.S. population; it is 94% white and better educated than the general public, with a lower percentage of smokers than in the Six City Study. The (crude) death rate during the 7.25 years of follow-up was just under 1% per year, which is about 20% lower than expected for the white population of the U.S. in 1985, at the average age reported by Pope et al. In contrast, the corresponding rates for the Six- Cities study (Dockery et al., 1993) discussed above tended to be higher than the U.S. average. In spite of these differences, the cause specific ratios for smoking are not signficantly different between the ACS and Six-Cities studies.

No mention was made of residence histories for the decedents; matching was done on residence location at entry to the study. The 1979 to 1981 pollution values were assumed to be representative of long-term cumulative exposures, in keeping with the objective of analyzing chronic effects. However, the previous decade was one of extensive pollution cleanup in most of the nation's dirtiest cities (TSP dropped by a factor of 2 in New York City, for example [Ferrand, 1978]). In contrast, air quality would have remained relatively constant in cities that already met the standards. Thus, it is reasonable to expect that the contrast between "clean" and "dirty" cities would have been greater in 1970 than in 1980. For example, the ranges of TSP and SO_4^{2-} across the U.S. in 1970 were from 40 to 224 and from 3 to 28 $\mu g/m^3$, respectively (Lipfert, 1978). In 1980, these ranges decreased to 41-142 and 2-17 $\mu g/m^3$ (Lipfert, 1993), which suggests that the dirtiest cities became cleaner while the "clean" cities stayed about the same. The change in pollution range is about a factor of 1.8. If the excess mortality found in this study were in fact due to cumulative exposures, the regression coefficients would have been biased upward (in terms of relative risk per $\mu g/m^3$) by using the more recent data. The typically long latency period for

lung cancer (ca. 20 yr.) suggests that data on prior exposures may be particularly important for this cause of death.

The adjusted total mortality risk ratios (computed for the range of the pollution variables) were 1.15 (95% CL = 1.09 to 1.22) for sulfates and 1.17 (95% CL = 1.09 to 1.26) for $PM_{2.5}$. When expressed as log-linear regression coefficients, these values were quite similar for both pollution measures: 0.0070 (0.0014) per $\mu g/m^3$ for SO_4^{2-} and 0.0064 (0.0015) for $PM_{2.5}$, suggesting that particle chemistry may be relatively unimportant as an independent risk factor (it is possible that the SO_4^{2-} results have been biased high by the presence of filter artifacts). Pope et al. (1995b) found that the pollution coefficients were reduced by 10 to 15% when variables for climate extremes were added to the model. Expressed as the percentage of mortality associated with air pollution at the mean values and corrected for filter artifact for SO_4^{2-} using the data of Lipfert (1994c), this study found mean effects of about 5% for sulfate and 12% for $PM_{2.5}$. No significant excess mortality for the "other" causes of death was attributed to air pollution in this study.

Pope et al. (1995b) found very consistent pollution risks for males and females and for ever-smokers and never-smokers for all-cause mortality. However, the relative risks for air pollution were slightly higher for females for cardiopulmonary causes of death. The lung cancer- sulfate association was only significant for males, except for male never-smokers.

The ACS study is unique in having controlled at least partly for passive smoking exposure. Passive smoking results were not reported and compared with the air pollution risks.

The results of the American Cancer Society prospective study were qualitatively consistent with those of the Six City study with regard to their findings for sulfates and fine particles; relative standard errors were smaller, as expected because of the substantially larger database. However, no other pollutants were investigated in the ACS analysis, so that it was not possible to provide the type of pollutant comparison given in Table 12-18. In addition, the ACS regression coefficients were about 1/4 to 1/2 of the corresponding Six City values and were much closer to the corresponding values obtained in various acute mortality studies. Thus it is not clear to what extent chronic effects (as opposed to integrated acute effects) are indicated by these results and to what extent the limited air quality data base used was responsible for this outcome.

Summary and Conclusions from Prospective Studies

Table 12-16 summarizes the three newer prospective studies considered here. The California and Six-City studies have relatively small sample sizes and inadequate degrees of freedom, which partially offsets the specificity gained by considering individuals instead of population groups. The two early studies not shown in this table were largely inconclusive and the studies of California nonsmokers by Abbey et al. (1991a, 1995a) that had the spatially most representative cumulative exposure estimates for TSP found no significant mortality effects of previous air pollution exposure. The Six Cities and ACS studies agree in their findings of strong associations between fine particles and excess mortality while the Abbey et al. (1991a, 1995a) studies had no data on fine particles. However, the ACS study did not systematically evaluate the effects of other copollutants. In addition, the timing of the critical exposures remains an open question as does the question of thresholds. It is also important that a range of pollutants be considered in both chronic and acute studies, since it is possible that acute effects may be exhibited by one pollutant and chronic effects by another. Lipfert and Wyzga (1995b) also discuss the studies using elasticity as an index of risk.

12.4.1.4 Assessment of Long-Term Studies

Previous Summaries of Cross-Sectional Studies

There have been many previous reviews and summaries of air pollution-mortality studies (Ricci and Wyzga, 1983; Lipfert, 1978, 1980b, 1985; International Electric Research Exchange, 1981; Evans et al., 1984b; Lave and Seskin, 1970; Cooper and Hamilton, 1979; Thibodeau et al., 1980; Ware et al., 1981). With respect to cross-sectional studies, Ware et al. (1981) concluded that "...The model can only be approximately correct, the surrogate explanatory variables can never lead to an adequate adjusted analysis, and it is impossible to separate associations of mortality rate with pollutant and confounding variables. This group of studies, in our opinion, provides no reliable evidence for assessing the health effects of sulfur dioxide and particulates...."

Comparison of Prospective and Population-based Cross-Sectional Study Results

The literature on long-term health effects of air pollution has been substantially enriched by the publication of the recent prospective studies. Their ability to stratify by smoking habit or

occupational exposure provides valuable information not previously available. These studies also provide a basis with which to evaluate the reasonableness of the "ecologic assumptions" that are required in order to interpret population-based studies. In this section, we consider the two types of studies on an equal footing, following the admonition of Greenland and Robins (1994b) that ecological studies should not be discounted just because they are ecological.

Table 12-19 compares regression coefficients from the two prospective studies that reported significant pollution risks with corresponding estimates made by Lipfert (1993) on an "ecologic" basis, i.e., using SMSA-wide mortality rates. Pope et al. (1995b) introduced this concept by comparing age-race-sex-adjusted SMSA mortality rates with their prospective findings, but without adjusting the SMSA-wide values for cofactors such as smoking or education. They noted the similarity in relative risk estimates between their prospective study findings and the SMSA-wide "ecologic" estimates, but they did not discuss whether the risks predicted by ecological studies would drop substantially if the equivalent confounding variables had been considered in both types of studies. Table 12-19 also makes this comparison and goes on to show how the ecologic estimates of the pollution effects diminish and become negative and/or non-significant as additional cofactors are entered into the regression model. Each of these factors has been shown (by others) to exert an influence on health, and all of them were significant in the ecologic model except drinking water hardness (for which t=1.6). This comparison suggests that the mortality risks assigned to air pollution by the prospective studies may have changed had individual data on additional risk

TABLE 12-19. COMPARISON OF LOG-LINEAR REGRESSION COEFFICIENTS FROM PROSPECTIVE AND "ECOLOGIC" ANALYSES FOR U.S. METROPOLITAN AREAS

Factors Accounted For	SO_4^{2-} coeff. (SE)	FP coeff. (SE)
A. Prospective studies		
1. Dockery et al. (1993)	(n=6)	(n=6)
age, sex, active smoking, body mass, education.	**0.0308 (0.011)**	**0.0124 (0.005)**
2. Pope et al. (1995b)	(n=151)	(n=50)
age, sex, race, active & passive[a] smoking, education[a], body mass[a], alcohol[a], occupational exposure[a]	**0.007 (0.0014)**	**0.0064 (0.0015)**
B. "Ecologic" regressions[b]	(n=149)	(n=63)
1. **age, race**	**0.0092 (0.0019)**	**0.0048 (0.0019)**
2. **age, race,** smoking	**0.0040 (0.00083)**	**0.0048 (0.00195)**
3. **age, race,** smoking, **education**	**0.0058 (0.00195)**	0.0018 (0.00195)
4. **age, race, smoking, education, migration**	-0.00044 (0.0021)	0.00012 (0.0016)
5. **age, rage, smoking, education, migration,** drinking water hardness	-0.00055 (0.0021)	0.00035 (0.0016)

Bold factors are significant ($p < 0.05$).
[a]Significance of cofactors not stated.
[b]Data from Lipfert, 1993.

factors been available and included in the analysis. If the additional significant risk factors were not confounded with air pollution, then the pollution effect would probably have been found more significant even if unchanged. On the other hand, including correlated risk factors could have either diminished or even increased the estimated effect attributed to air pollution.

It is also interesting that introduction of the smoking variable (statewide cigarette sales) into the ecologic regressions had little or no effect on the pollution coefficients, whereas the other variables had relatively large effects (the correlation between this smoking variable and SO_4^{2-} was

only 0.15). The relative risk corresponding to the ecologic smoking risk coefficient was somewhat less than those found by the prospective studies, probably because this variable is a poor surrogate for individual smoking rates.

Figures 12-9a to 12-9c were prepared to illustrate the overlapping confidence intervals of the various studies using mortality data ca. 1980 and later. For SO_4^{2-}, Figure 12-9a, the two prospective studies and Ozkaynak and Thurston's (1987) ecological study overlap, mainly because of the very wide confidence limits of the Six City Study. However, all of these studies accounted for a somewhat limited range of potential confounding variables; the 1980 SMSA study by Lipfert (1993) found SO_4^{2-} to lose significance when additional variables were entered into the model. More overlap is shown for $PM_{2.5}$ (Figure 12-9b), even though significance was not achieved with either ecological study. Overlapping confidence intervals are also seen with TSP (Figure 12-9c), including the California prospective study. These plots thus suggest that much of the apparent contrast among studies could be due to chance variation.

The important contribution of the prospective studies is the proper accounting for individual risk factors, mainly smoking. The question thus arises, could inadequate control for smoking in an ecological study lead to an underestimate of the air pollution relationship? This would require a negative correlation between smoking and air pollution. However, based on state-level data, the correlations between smoking and both SO_4^{2-} and $PM_{2.5}$ are weakly positive. Thus it does not appear that inadequate control for smoking explains the difference in results. One is thus led to the conclusion that either some other factor is negatively correlated with air pollution or that the prospective studies are affected by some confounder that is more important at the individual level than at the community-average level. Of course, much of the range in results seen in these plots could also be due to chance.

Concluding Discussion

Referring back to the original goals of long-term mortality studies, several questions appear worthy of reconsideration:

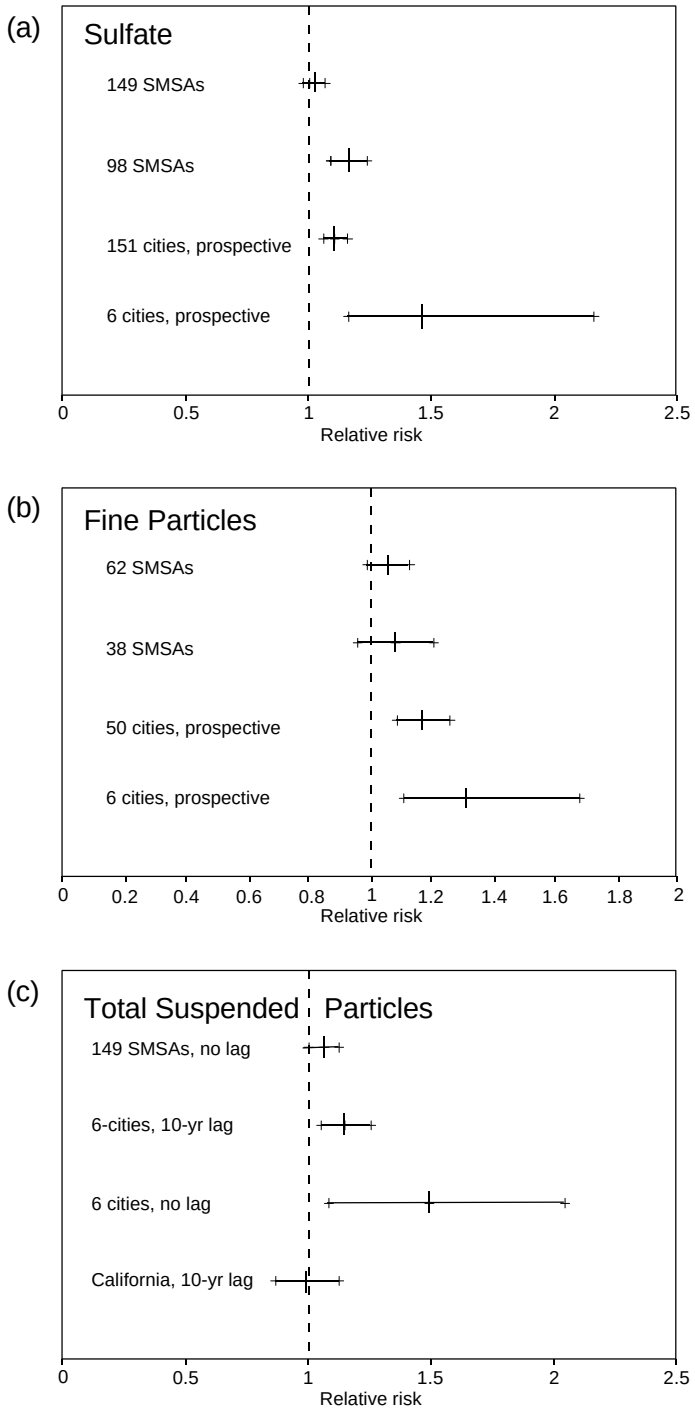

Figure 12-9. Comparison of relative risks of air pollution exposure in long-term population-based and prospective studies: (a) 15 μg/m^3 sulfate, (b) 25 μg/m^3 $PM_{2.5}$, (c) 100 μg/m^3 total suspended particles.

Source: Lipfert (1993), Dockery et al. (1993), Ozkaynak and Thurston (1987), Abbey et al. (1993), Pope et al. (1995b).

1. Have potentially important confounding variables been omitted? While many factors are known or believed to affect mortality rates, only those factors that are known to be correlated with air pollution and have effects at least as large as the identified air pollution factors are candidates for omitted significant confounders. Some of these factors were investigated in population-based cross-sectional studies, including selective migration (population loss and gain), lifestyle (diet, physical fitness), socioeconomic status (income, education, occupation associated with potential exposure to air pollution), and other environmental factors (drinking water hardness). As shown in Figure 12-7, including these factors greatly reduces the variability in covariate-adjusted community mortality rates, but does not eliminate the relationship between mortality and long-term fine particle concentrations. Similar adjustments suggest somewhat greater potential for spatial confounding with sulfates in cross-sectional studies than with fine particles. Analyses of the prospective cohort studies have so far included fewer of these factors, and even when the studies have included important individual risk factors such as potential exposure to environmental tobacco smoke, the results for these factors have not yet been reported (Abbey et al., 1991a; Pope et al., 1995b). While it is not likely that the prospective cohort studies have overlooked plausible confounding factors that can account for the large effects attributed to air pollution, there may be some further adjustments in the estimated magnitude of these effects as additional individual and community risk factors are included in the analyses.

2. Can the most important pollutant species be identified? Analyses using data on long-term average concentrations of multiple pollutants have been carried out for many of the population-based cross-sectional studies. Estimates of regression coefficients for PM may be relatively less sensitive to confounding with copollutants in these studies than in the acute mortality studies because there are differences in sources of PM and of other air pollutants across different communities, therefore less collinearity across a spatial cross-section of communities than in air pollution time series data within a particular community. Some investigators have argued that the relative similarity of estimated PM effects in daily time series studies for different communities in which PM is the only air pollutant in the model is an indication that the PM effects are not seriously confounded with those of other air pollutants. However, this argument ignores potential differences in acute vs. chronic effects of different pollutants (see next paragraph).

   The issue of confounding with copollutants has not been resolved for the prospective cohort studies. Abbey et al. (1991a) found no significant association between all-disease mortality and TSP or O3. Dockery et al. (1993) found a very clear gradient of mortality that was rank-ordered with levels of air pollution in six cities, but since many pollutants were similarly rank-ordered across the six cities, it was not possible to say which one(s) were primarily responsible. The best relationships were obtained with fine particles, and almost equally good relationships were found between excess mortality and either sulfate or non-sulfate components of fine particles. However, except for Topeka where the coarse inhalable particles were believed to be primarily of crustal origin, a similarly good relationship was found between excess mortality and inhalable particles or the

coarse particle component of inhalable particles. The ACS study (Pope et al., 1995b) was analysed specifically to test hypotheses about combustion particles, so used only PM2.5 and SO4 as single air pollution indices. Analytical strategies that could have allowed greater separation of air pollutant effects have not yet been applied to the prospective cohort studies.

3. Can the time scales for long-term exposure effects be evaluated? This question has not been resolved by the analyses published so far. Almost all of the population-based cross-sectional studies used long-term average concentrations over the preceding few years or preceding decade, and the few reported analyses on long-term time-lagged exposure were not conclusive. The prospective cohort studies of Abbey et al. (1991a) have also used only long-term community average concentrations. The analyses by Dockery et al. (1993) used only the average pollutant concentrations through the final year of the study period, and it is interesting that the best-fitting pollutants (inhable particles, fine particles, and sulfates) had the shortest period of monitoring data. The ACS (Pope et al., 1995b) pollution data set was even more limited, since only one year of sulfate data was used, and the fine particle data were limited to a subset of the locations used in the sulfate data set and contained only a few years of data.

   Careful review of the published studies indicated a lack of attention to this issue. Long-term mortality studies have the potential to infer temporal relationships based on characterization of changes in pollution levels over time. For example, mortality has the following conceptual time scales:
   - Mortality associated with acute episodic exposures during different seasons;
   - Mortality associated with changes in air pollution due to changes in primary source emissions (for example, Utah Valley in 1987);
   - Mortality associated with sub-chronic exposures over the preceding year or few years;
   - Mortality associated with long-term exposures over the preceding decade or decades.

   Historic air pollution data bases allow construction of air pollution exposure indices at each time scale. For the purposes of such inferences, daily time series, every-other-day time series, every-sixth-day time series, and even monthly time series data could have been used. Furthermore, these time-varying indices could have been constructed using the historic community air pollution data for individual decedents and survivors in the prospective cohort studies, allowing a substantially larger amount of subject-specific air pollution exposure information (in statistical terms, allowing a large number of degrees of freedom for air pollution, rather than just 6 degrees of freedom in the Six City Study for example).

   Published analyses do not allow a clear separation of the short-term and long-term effects of pollution exposure. This also complicates the attribution of mortality to specific pollutants, since excess mortality may be hypothetically attributable to short-term episodic exposures to one pollutant and to long-term or chronic exposures to another pollutant or PM component that may be either an independent additive risk

factor to the short-term pollutant factor, or interactive with the short-term pollutant as a contributing or predisposing factor. Since the different pollutant components may be correlated with each other, the pollutant effects and the time scale effects may be confounded.

4. Is it possible to identify pollutant thresholds that might be helpful in health assessments? Some of the cross-sectional studies have found suggestions of thresholds. However, none of these suggestions can be regarded as robust, and it is possible that uncertainties in the variables selected as proxies for non-pollution effects may have contributed to these findings. Measurement error in pollution variables also complicates the search for potential threshold effects, but the statistical relationship may be stronger and thresholds more easily detected when more reliable exposure data are used in the analyses, for example for those pollutants for which personal exposure and ambient measurements are believed to be more closely related such as sulfates (see discussion in Chapter 7).

   Model specification searches for thresholds have not been reported for prospective cohort studies. The problems of measurement error that complicate threshold detection in the population-based studies have a somewhat different character for the prospective studies. The first problem is that individual risk factors may be measured with error (for example, by failing to report changes in risk factors over time). Another aspect of measurement error is that measured ambient exposures may be correlated with individual risk factors, including indoor air pollution, that also affect health status and potential susceptibility to outdoor air pollution. While only a few such factors can be measured in the daily time series studies (such as age, race, sex, location of residence, place of death), the specification of individual risk factors is one of the principal advantages of the prospective study. Conversely, the possible misspecification or omission of individual risk factors is one of the principal disadvantages of the prospective design, and one the most difficult problems in using epidemiology data to identify thresholds for use in health assessments.

Thus, it appears that, as with most epidemiology, consistency among studies of widely varying design must be sought in order to respond to the shortcomings that were noted earlier, since different designs have different strengths and weaknesses. Among the long-term exposure studies, it is important to find consistency in terms of geographic scale, time periods, pollutant levels, and regional locations. It will also be important to contrast the findings from short- and long- term exposures and to examine coherence among various health endpoints.

At this time, the long-term studies provide support for the existence of short-term PM exposure effects an mortality which may not be completely canceled by decreases below normal rates. They also point toward the likelihood of chronic PM exposure effects above and beyond

the simple summation of acute mortality effects. However, they are equivocal as to all the specific pollutants involved, and they do not exclude the existence of pollutant thresholds, and quantitative estimates of cumulative PM exposure effects beyond acute impacts cannot yet be confidently stated.

12.4.2 Morbidity Effects of Long-Term Particulate Matter Exposure

Acute exposures to PM are associated with increased reporting of respiratory symptoms and with small decrements in several measures of lung function (Section 12.3.2.3). As a consequence, cross-sectional studies of the relationship between long-term exposure to PM (or any air pollutant) and consequent chronic effects on respiratory function and/or symptoms may be limited by the inability to control for effects of recent exposures on function and symptoms. Moreover, such studies are further handicapped by: (1) limited ability to characterize accurately lifetime exposure to PM other than through "area-based" ecological assignments or assignments inferred from short-term, acute measurements; (2) their inherent limited ability to characterize correctly other relevant exposure histories (e.g., past histories of respiratory illnesses, passive exposure to tobacco smoke products, active smoking in older subjects); and (3) the fact that the effects to be detected in long term exposure studies may be small in comparison to other sources of variation.

Longitudinal studies offer numerous obvious advantages over cross-sectional studies in terms of characterization of PM exposure and relevant covariates. Nonetheless, to the extent that such studies base their inferences regarding occurrence of long-term morbidity on effects observed over relatively short durations of cohort follow-up (e.g., respiratory illness incidence in relation to ambient PM, short-term relationship between ambient PM and lung function, etc.), their results need to be viewed with circumspection. These approaches do not definitively establish effects of long-term exposure, but only suggest the coherence of the possibility of such long-term effects. Optimal longitudinal studies would provide data on incident chronic conditions such as physician diagnosed asthma and/or evidence for altered patterns of lung function growth and decline for children and adults, respectively. Table 12-20 shows the incidence of selected cardiorespiratory disorders by age and by geographic region.

12.4.2.1 Respiratory Illness Studies

Studies of Children

The 1982 Criteria Document (U.S. Environmental Protection Agency, 1982a) indicated that apparent quantitative relationships between air pollution and lower respiratory tract illness in children were reported by Lunn et al. (1967), who studied respiratory illnesses in 5- and 6-year old school children living in four areas of Sheffield, England. Positive associations were found between air pollution concentrations and both upper and lower respiratory illness. Lower respiratory illness was 33 to 56% more frequent in the higher pollution areas than in the low-pollution area ($p < 0.005$). Also, decrements in lung function, measured by spirometry tests, were closely associated with respiratory disease symptom rates. Lunn et al. (1970) also reported results for 11-year-old children studied in 1963 to 1964 that were similar to those found earlier for the younger group. On the basis of the results reported, it appears that increased frequency of lower respiratory symptoms and decreased lung function in children may occur with long-term exposures to annual BS levels in the range of 230 to 301 $\mu g/m^3$ and SO_2 levels of 181 to 275 $\mu g/m^3$. However, it was noted that these are only very approximate observed-effect levels because of uncertainties associated with estimating PM mass based on BS readings. Also, it could not then be concluded, based on the 1968 follow-up study, that no-effect levels were demonstrated for BS levels in the range of 48 to 169 $\mu g/m^3$ because of: (1) the likely insufficient power of the study to have detected small changes given the size of the population cohorts studied, and (2) the lack of site-specific calibration of the BS mass readings at the time of the later (1968) study. In summary, the Lunn et al. (1967) study provided the clearest evidence cited in the 1982 EPA Criteria Document for associations between both pulmonary function decrements

TABLE 12-20. INCIDENCE OF SELECTED CARDIORESPIRATORY DISORDERS BY AGE AND BY GEOGRAPHIC REGION (reported as incidence per thousand population and as number of cases in thousands)

		Age				Regional			
Chronic Condition/Disease	All Ages	Under 45	45-64	Over 65	Over 75	NE	MW	S	W
COPD									
Incidence/1,000 persons	61	50	63	104	107	56	63	63	61
No. cases × 1,000	15,400	8,650	3,550	3,210	1,200				
Asthma									
Incidence/1,000 persons	49	52	45	40	34	48	49	48	52
No. cases × 1,000	12,370	9,000	2,180	1,230	420				
Heart Disease									
Incidence/1,000 persons	86	29	135	325	404	89	84	93	74
No. cases × 1,000	21,600	5,050	6,540	10,000	4,980				
HD-ischemic									
Incidence/1,000 persons	32	3	61	153	184	37	29	37	24
No. cases × 1,000	8,160	490	2,970	4,702	2,270				
HD-rhythmic									
Incidence/1,000 persons	33	20	44	83	104	33	35	32	31
No. cases × 1,000	8,160	3,500	970	2,550	1,275				
Hypertension									
Incidence/1,000 persons	111	34	226	358	352	106	115	123	91
No. cases × 1,000	27,820	5,830	10,980	11,000	4,300				

Source: National Center for Health Statistics (1994c).

and increased respiratory illnesses in children and chronic exposure to specific ambient air levels of PM and SO_2.

In another key study reviewed in the second Addendum to the 1982 Criteria Document, Ware et al. (1986) had evaluated respiratory illness and symptoms in children as part of the Harvard Six-City Study. The earlier survey included questions on presence of bronchitis, chronic cough, chest illness, persistent wheeze and asthma. The analysis was restricted to white children (6 to 9 years old) enrolled during one of the first three visits to each city. At least one centrally located air monitoring station established in each community measuring TSP, SO_2, water soluble sulfate, NO_2, and O_3 starting in 1974. The cities of St. Louis, Steubenville and Kingston-Harriman were divided into two regions based on exposure. Multiple logistic regression coefficients were significant for cough, bronchitis, and lower respiratory illness for both TSP and water soluble sulfate. The between city coefficients for TSP ($\mu g/m^3$) were .0101 (.0018) for cough, .0103 (.0046) for bronchitis, and .0076 (.0035) for lower respiratory illness. TSP coefficients for within city analyses tended to be negative.

Dockery et al. (1989) studied respiratory symptoms in 10 to 12 year old white children in the same six U.S. communities as Ware et al. (1986): Watertown, MA; St. Louis, MO; Portage, WI; Kingston-Harriman, TN; Steubenville, OH; and Topeka, KS. A cross-sectional survey done in 1980 to 1981 included questions on presence of bronchitis, chronic cough, chest illness, persistent wheeze and asthma. The analysis was restricted to 5,422 white children. Dta on TSP, SO_2, NO_2, and O_3 were obtained from a central air monitoring station in each community starting in 1974. Starting in 1978, dichotomous samplers were used to measure PM_{15}. Multiple logistic regression analyses were performed for each health endpoint. The estimated relative odds of bronchitis comparing the most polluted community to the least, was 2.5 (1.1 to 6.1). This corresponded to a 38.7 $\mu g/m^3$ increase in the PM_{15} level. For chronic cough, the odds ratio was 3.7 (1.0 to 13.5); and, for chest illness, it was 2.3 (0.8 to 6.7). The odds ratios corresponding to the other pollutants including TSP, $PM_{2.5}$, sulfate fraction, SO_2, NO_2, and O_3 were not significant, although all were greater than 1.

Data for a cohort of white children aged 7 to 11 from the same Six-City Study were further analyzed by Neas et al. (1994). Respiratory illness history and other background information were collected via a parent-completed questionnaire between September, 1983 and June, 1986.

A stratified one-third random sample of the questionnaire respondents (300 to 350 households per city) was invited to participate in an indoor air quality measurements study. Indoor air quality was measured during two consecutive 1-week sampling periods in both winter and summer; in which respirable particulates ($PM_{2.5}$) and NO_2 were measured. Health endpoints reported by questionnaire included shortness of breath, persistent wheeze, chronic cough, bronchitis, asthma, hayfever, earache, and chest illness. Odds ratios (OR) were calculated using multiple logistic regression for an increase of 30 $\mu g/m^3$ in $PM_{2.5}$, after adjusting for gender, age, parental education, parental history of asthma, and city. Most of the health endpoints showed little effect from $PM_{2.5}$ except for bronchitis (OR = 1.18, CI = 0.99, 1.42) and any lower respiratory symptom (OR = 1.13, CI = 0.99, 1.30). However, because no ambient PM data from the Six-City Study were used in the Neas et al. (1994) analyses, the implications of their results for ambient PM exposures are unclear.

Dockery et al. (1996) studied respiratory symptoms among 13,369 white children (8 to 12 years) surveyed between 1988 and 1990 in 24 North American communities chosen based on a gradient of acidic air pollution. Pollutants monitored included particulate acidity, total sulfate, $PM_{2.1}$, PM_{10}, SO_2, and O_3 (Spengler et al. 1996). A two-stage logistic regression model was used to analyze symptoms adjusting for gender, history of allergies, parental asthma, parental education, and current smoking in the home. Children living in communities with the highest levels of particle strong acidity were significantly more likely (OR = 1.66, 95% CI = 1.11, 2.48) to report at least one episode of bronchitis in the past year compared to children living in communities with the lowest levels of acidity. Fine particulate sulfate was also associated with increased bronchitis. For $PM_{2.1}$ and PM_{10}, respectively, the odds ratios for bronchitis were 1.50 (95% CI = 0.91, 2.47) and 1.50 (95% CI = 0.93, 2.43), respectively. No other respiratory symptoms were significantly associated with any of the pollutants, including no evidence of asthma or asthmatic symptoms being associated with the measured pollutants. No sensitive subgroups were identified. Strong correlations between several pollutants in this study, especially particle strong acidity in the sulfate (r = 0.90) and $PM_{2.1}$ (r = 0.82), make it difficult to distinguish the indicator of interest.

Stern et al. (1994) studied respiratory illness and lung function in five southwestern Ontario towns (Blenheim, Ridgetown, Tillsonburg, Strathroy, and Wallaceburg) and five in south-central

Saskatchewan (Esterhazy, Melville, Melfort, Weyburn, and Yorkton. Self-administered parental questionnaires were distributed between October 1985 and March 1986. Pollution monitoring started in late 1985 included SO_2, NO_2, O_3, and PM_{10} (measured once every six days in the Ontario towns and every three days in the Saskatchewan towns). Odds ratios were computed (presumably using multiple logistic regression with a random effects model) comparing the endpoints of cough, phlegm, wheeze, asthma, bronchitis, and chest illness for the Ontario towns versus the Saskatchewan towns. No significant differences were found, even after adjusting for gender, parental smoking, parental education, and gas cooking. Actual exposure estimates for the individual towns were not used. The overall mean PM_{10} level for the Ontario towns was 23.0 $\mu g/m^3$ versus 18.0 $\mu g/m^3$ for Saskatchewan.

Studies of Adults

The 1982 Criteria Document (U.S. Environmental Protection Agency, 1982a) discussed a series of studies, reported on from the early 1960s to the mid-1970s (Ferris and Anderson, 1962; Kenline, 1962; Anderson et al., 1964; Ferris et al., 1967, 1971, 1976). The initial study involved comparison of three areas within a pulp-mill town (Berlin, New Hampshire). In the original prevalence study (Ferris and Anderson, 1962; Anderson et al., 1964), no association was found between questionnaire-determined symptoms and lung function tests assessed in the winter and spring of 1961 in the three areas with differing pollution levels, after standardizing for cigarette smoking. The study was later extended to compare Berlin, NH, with the cleaner city of Chilliwack, BC, in Canada (Anderson and Ferris, 1965). The prevalence of chronic respiratory disease was greater in Berlin, but the authors concluded that this difference was due to interactions between age and smoking habits within the respective populations.

The Berlin, NH, population was followed up in 1967 and again in 1973 (Ferris et al., 1971, 1976). During 1961 to 1967, all measured indicators of air pollution fell (e.g., TSP from about 180 $\mu g/m^3$ in 1961 to 131 $\mu g/m^3$ in 1967). In the 1973 follow-up, sulfation rates nearly doubled from the 1967 level (0.469 to 0.901 mg $SO_3/100\ cm^2$ day) while TSP values fell from 131 to 80 $\mu g/m^3$. Only limited SO_2 data were available (i.e., the mean of a series of 8-h samples for selected weeks.) During the 1961 to 1967 period, standardized respiratory symptom rates decreased and lung function also improved. Between 1967 to 1973, age-sex standardized respiratory symptom

rates and age-sex-height standardized pulmonary function levels were unchanged. Although some of the testing was done during spring versus summer in different comparison years, Ferris and coworkers tried to rule out seasonal effects by retesting some subjects in both seasons during one year and found no significant differences in test results. Given that the same set of investigators, using the same standardized procedures, conducted the symptom surveys and pulmonary function tests over the entire course of these studies, it is unlikely that the health endpoint improvements seen in the Berlin study population were due to variations in testing procedures; rather, they appear attributable to decreases in TSP levels from 180 to 131 $\mu g/m^3$. The relatively small changes observed and limited aerometric data available, however, argue for caution in placing much weight on these findings as quantitative indices for effect or no-effect levels for health changes in adults associated with chronic exposures to PM measured as TSP.

The earlier 1982 criteria review (U.S. Environmental Protection Agency, 1982a) also assessed a cross-sectional study conducted by Bouhuys et al. (1978) in Ansonia (urban) and in Lebanon (rural), two Connecticut towns in which differences in respiratory and pulmonary function were examined in 3,056 subjects (adults and children). No differences were found between Ansonia and Lebanon for chronic bronchitis prevalence rates, but a history of bronchial asthma was noted as being highly significant for male resident of Lebanon (the cleaner town) as compared to Ansonia (the higher-pollution area). Nor were any significant differences observed between the communities for pulmonary function tests adjusted for sex, age, height and smoking habits. However, prevalence for three of five symptoms (cough, phlegm, and plus one dyspnea) were significantly ($p < 0.001$) higher for adult non-smokers in Ansonia. Overall, the mix of positive and negative health effect results make it difficult to interpret this cross-sectional study.

Numerous published studies have attempted to relate chronic respiratory health effects to ambient pollutants such as PM and O_3 (Hodgkin et al., 1984; Euler et al., 1987, 1988; Abbey et al., 1991a,b; 1995a,b,c). From among these, the series of publications from the Adventist Health Smog Study (AHSMOG) (Hodgkin et al., 1984; Euler et al., 1987, 1988; Abbey et al., 1991a,b) are discussed first below.

The basic population for these studies represents California-resident, Seventh-Day Adventists aged 25 years who had lived 11 years or longer (as of August 1976) in either a high-oxidant-polluted area (the South Coast Air Basin encompassing Los Angeles and vicinity and a

portion of the nearby Southeast Desert Air Basin) or a low-pollution area (San Francisco or San Diego). This sample was supplemented by an additional group of subjects who met the 11-year residence requirement but came from low-exposure rural areas in California. The total baseline sample (March 1977) comprised 8,572 individuals, of whom 7,267 enrolled. From this group, 109 current smokers and 492 subjects who had lived outside of the designated areas for a portion of the previous 11 years were excluded. Detailed respiratory illness and occupational histories were obtained. In these studies, "COPD" refers to "definite chronic bronchitis", "definite emphysema", and "definite asthma" as defined by the study questionnaire. Measures of pulmonary function are not included.

California Air Resources Board (CARB) air monitoring system data for total oxidants, O_3, TSP, SO_2, NO_2, CO, and SO_4 (excluding 1973 to 1975) were used. Most (99%) of the subjects (excluding the rural supplement) lived close enough to the nearest CARB monitoring site to consider the CARB data as relatively reliable concentration estimates for the above listed ambient pollutants at their residence. Concentrations at the monitors were interpolated to the centroid of each residential zip code from the three nearest monitoring sites with the use of a $1/R^2$ interpolation. Subsequent development of exposure indices took account of improvements in CARB data after 1973.

The initial report from this study (Hodgkin et al., 1984) was summarized in the 1986 Ozone Criteria Document (U.S. Environmental Protection Agency, 1986c). Based upon a multiple logistic regression that adjusted for smoking, occupation, race, sex, age, and education, it was estimated that residence in the South Coast Air Basin conferred a 15% increase in risk for prevalent COPD. No estimates of exposure were provided, and the data were considered to be of limited utility.

Next, Euler et al. (1988) assessed the risk of chronic respiratory disease symptoms due to long-term exposure to ambient levels of TSP, oxidants, SO_2, and NO_2. Symptoms were ascertained for 8,572 Southern California Seventh-Day Adventists (nonsmokers—25 years and older) who had lived 11 years or longer in their 1977 residential area by using the National Heart, Lung, and Blood Institute questionnaire. Tobacco smoking (active and passive) and occupational exposures were assessed by questionnaires, as were lifestyle characteristics relative to pollution exposure (e.g., such as time spent outside and residence history). For each of the 7,336

participants who responded and qualified for analysis, cumulative exposures to each pollutant were estimated using monthly residence zip code histories and interpolated exposures from state air monitoring stations.

Multiple logistic regression analyses were conducted for pollutants individually and together with eight covariables (environmental tobacco smoke exposure at home and at work, past smoking, occupational exposure, sex, age, race, and education). Statistically significant associations with chronic respiratory symptoms were seen for: (a) SO_2 ($p = 0.03$), relative risk of 1.18 for 13% of the study population with 500 h/year of exposure above 0.04 ppm; (b) oxidants ($p < 0.004$) relative risk of 1.20 for 18% with 750 h/year above 0.1 ppm; and (c) TSP ($p < 0.00001$), relative risk of 1.22 for 25% with 750 h/year above 200 $\mu g/m^3$. When these pollutant measures were analyzed together, only TSP showed statistical significance ($p < 0.01$). Persons working with smokers for 10 years had relative risks of 1.11 and those living with a smoker for 10 years had relative risks of 1.07.

Major improvements in the exposure assessment methods used were presented by Abbey et al (1991a). Previous exposure estimates were refined by computation of "excess concentrations" (concentration minus cutoff, summed over all relevant time periods and corrected for missing data). Exposures also were corrected for time spent at work and time away from residence, with estimates provided for the environments where work occurred and for geographic areas away from residence. The quality of the interpolations (in terms of distance of monitor from residence zip codes) was also evaluated and incorporated into the estimates. Adjustments were made for time spent indoors by individuals and new indices were developed that were based on O_3, rather than on total oxidants. Comparison of actual versus interpolated cumulative exceedance frequencies and mean concentrations at monitoring stations (1985 through 1986) for TSP and O_3 were assessed. The actual versus interpolated 2-y mean concentrations did not differ significantly and were correlated with a Pearson correlation coefficient of 0.78 for TSP and 0.87 for O_3.

The above estimates were applied to data that included 6 years of follow-up of the study population (Abbey et al., 1991b). This analysis focused on incident occurrence of obstructive airways disease (AOD—same definition as for COPD above). Incident symptoms of AOD were significantly associated with hours above several TSP thresholds, but not with hours above any

O_3 threshold (i.e., above 10 pphm ozone - OZ (10)). Incidence of definite symptoms of AOD and chronic bronchitis were statistically significantly ($P < 0.05$) elevated for average annual hours in excess of 100, 150, and 200 $\mu g/m^3$, i.e., TSP (200), and mean concentrations of TSP but not for 60 $\mu g/m^3$. For incidence of asthma, significantly elevated risks were found only for average annual hours above thresholds of 150 and 200 $\mu g/m^3$, i.e., TSP (200). Relative risks for concentrations above 200 $\mu g/m^3$ of TSP for bronchitis were 1.33 (95% CL = 1.07 to 1.81); and for asthma 1.74 (95% CL = 1.11 to 2.92). Cumulative incidence estimates were adjusted with the use of Cox proportional hazard models for the same variables noted in the original publication of Hodgkin et al. (1984), as well as the presence of possible symptoms in 1977 and childhood respiratory illness history. None of the analyses included both O_3 and TSP thresholds. No data were provided on demographics of subjects available for the prospective analysis and their representativeness versus the entire base population.

Another analysis by Abbey et al. (1993) evaluated changes in respiratory symptom severity with the TSP and O_3 thresholds noted above. In this analysis, logistic regression, rather than Cox proportional hazard modeling, was used to assess cumulative incidence of components of the COPD/AOD complex; and multiple, linear regression was used to evaluate changes in symptom severity. When O_3 was considered alone, there was a trend toward increased risk of asthma for a 1,000-h average annual increment in the OZ (10) criterion (RR = 2.07, 95% CL = 0.98 to 4.89). This analysis suggested that recent ambient O_3 concentrations were more related to cumulative incidence than past concentrations. Change in asthma severity score was significantly associated with the 1977 to 1987 average annual exceedance frequency for O_3 thresholds of 10 and 12 pphm. No significant effects were found for COPD or bronchitis alone. In contrast to the above study of cumulative incidence, another analysis was done in which TSP (200) and OZ (10) were allowed to compete for entry into a model to evaluate asthma cumulative incidence and changes in severity. In the cumulative incidence model using exceedance frequencies (number of hours above threshold), TSP (200) entered before OZ (10); when average annual mean concentrations were used, O_3 entered before TSP. From this, the authors concluded that both TSP and O_3 were relevant to asthma cumulative incidence. In no case did both pollutants simultaneously remain significant in the same regression, and no interactions between TSP and O_3 were found for either metric. A similar result was found for change in asthma severity. As in previous analyses, TSP

(200) and OZ (10) exceedance frequencies (0.72) were highly correlated with their respective average annual mean concentrations (0.74).

Abbey et al. (1995a) analyzed the same cohort for development of airway obstructive disease (AOD), bronchitis, and asthma for the 1977 to 1987 period. Levels of TSP were monitored from 1973 to 1987; PM_{10} was estimated from site/seasonal-specific regressions on TSP for 1973 to 1987; and fine particles ($PM_{2.5}$) were estimated from airport visibility data for 1967 to 1987. Relative risks near 1.4 were found for areas with 42 days/year of TSP levels above 200 $\mu g/m^3$ and relative risks near 1.2 were found for 42 days/year of PM_{10} levels above 100 $\mu g/m^3$. The relative risks for an average annual increase of $PM_{2.5}$ above 45 $\mu g/m^3$ were not statistically significant. The use of cut-points makes it difficult to derive quantitative relationships between the health effects and the pollutants. Also, the authors note that the effects of TSP, PM_{10}, and $PM_{2.5}$ cannot be truly separated in this study since PM_{10} and $PM_{2.5}$ were indirectly estimated, whereas TSP was actually monitored and, also, because of the high correlation between them.

Abbey et al. (1995b) reanalyzed the same data using estimated concentrations as described by Abbey et al. (1995c). The same three dependent variables, AOD, bronchitis, and asthma, were used in the analysis along with the covariates of age, education, gender, and previous symptoms. The effect of $PM_{2.5}$ on new AOD was an estimated relative risk of 1.46 (95% CI of 0.84 to 2.46), and the effect on new bronchitis was 1.81 (95% CI of 0.98 to 3.25). Relative risks using PM_{10} and TSP were not given, but reported t-values suggested that TSP and PM_{10} were better predictors of all three endpoints. The authors attributed this difference to measurement error because all three pollutant measures were highly correlated.

Schwartz (1993b) analyzed data on respiratory illness diagnosed by a physician from the NHANES survey conducted from 1971 to 1974 on the non-institutionalized U.S. population aged 1 to 74. The survey used a complex design and the Schwartz analysis was restricted to 53 urban sampling units. Endpoints included asthma, bronchitis, respiratory illness and dyspnea. EPA's SAROAD data base was used to obtain data from population oriented monitors in the 53 areas. Average TSP concentrations ($\mu g/m^3$) for previous years were used as the exposure measure. No other pollutants were considered. Multiple logistic regression analysis was used that included terms for cigarette consumption per day, former smoking, age, race, and gender. The coefficient

for chronic bronchitis was .0068 (.0023) and for respiratory illness it was .0058 (.0019) (change in OR per $\mu g/m^3$ TSP). The coefficients were slightly larger when restricted to non-smokers.

Yano et al. (1990) studied chronic respiratory illness in females aged 30 to 59 in two cities in Japan. One city, Kanoya is 25 km from an active volcano, and the other, Tashiro, is 50 km from the volcano. Winter concentrations of TSP in Kanoya average 341 $\mu g/m^3$, whereas they average 119 $\mu g/m^3$ in Tashiro. Respiratory conditions were assessed using a Japanese version of the ATS-DLD questionnaire. No significant difference in rates of bronchitis, asthma, wheezing, or other related illnesses were found.

Ishikawa et al. (1969), which was reviewed in U.S. EPA (1982a), assessed the prevalence and severity of pulmonary emphysema by examining a series of postmortem lungs obtained from long-time residents in two cities: heavily industralized urban St. Louis, MO and agricultural Winnipeg, Canada. Three hundred adult lungs were collected for each city during the years 1960 to 1966. No attempt to correlate clinical signs and symptoms with pathoanatomic changes was undertaken. Air pollution emissions in one-thousand tons per year for sulfur oxides, nitrogen oxides, hydrocarbons, and "particulates" were respectively, 455, 138, 374, and 147 in St. Louis; and were respectively 36, 20, 62 and 82 on Winnipeg. In neither city were cases of severe emphysema observed in nonsmokers. There was more emphysema in the study in St. Louis than in Winnipeg, but the study does not provide any way to credibly associate the health observations specifically with PM exposure. Other more elevated pollutants or other factors may have played a role.

Some researchers used case-control approaches to study chronic respiratory system health effects in relationship to ambient pollutants such as PM. For example, Tzonou et al. (1992) studied the relation of urban living and tobacco smoking to COPD development in Athens, Greece. Their findings suggested that air pollution or another aspect of the urban environment can be an important contribution to the development of COPD. Specific PM levels were not studied. Katsouyanni et al. (1991) conducted a case-control study in Athens exploring the role of smoking and outdoor air pollution and their relationship to lung cancer. Air pollution levels were associated with an increased risk for lung cancer but the relative risk was small and not statistically significant. Xu et al. (1989) studied air pollutants and lung cancer in China and their findings suggested that smoking and environmental pollution combined to allow for elevated rates

of lung cancer mortality. In Poland, Jedrychowski et al. (1990) found similar findings as the above studies.

Rothman et al. (1991) reported that wildland firefighters experience a small cross-seasonal decline in pulmonary function and an increase in several respiratory symptoms. Hours of self-reported fire-fighting activity were used as a surrogate for fire smoke exposure. At wildland fires, concentrations of a variety of pulmonary irritants (including respirable PM, acrolein and formaldehyde) often exceed Occupational Safety and Health Administration (OSHA) permissible exposure limits. In a study by Shusterman et al. (1993) on smoke-related disorders in Alameda County, CA related to an October 20, 1991 grass fire in the Oakland-Berkeley hills, bronchospaitic and irritative reactions to smoke constituted more than half of the medical emergency visits related to the fire. Many of these patients had a history of asthma.

Chronic Respiratory Disease Studies Summary

The first three studies in Table 12-21 were based on a similar type of questionnaire but were done by Harvard University at three different times as part of the Six-City and 24-City Studies. The studies provide data on the relationship of chronic respiratory disease to PM.

TABLE 12-21. CHRONIC RESPIRATORY DISEASE STUDIES

Study	PM Type & No. Sites	PM Mean & Range	Overall Symptom Rate	Model Type	Other pollutants measured	Other Covariates	Other pollutants in model	Result* (Confidence Interval)
Ware et al. (1986) Study of respiratory symptoms in children in 6 cities in the U.S. Survey done 1974-1977	Daily monitoring of TSP, SO_2, O_3, and NO_2, at each city	City TSP means ranged from 39 to 114 µg/m^3	Cough, .08, Bronchitis .08, Lower resp. .19	Logistic regression	SO_2, NO_2, and O_3	Age, gender, parental education, maternal smoking	none	Cough 2.75 (1.92, 3.94) Bronchitis 2.80 (1.17, 7.03) Lower resp. 2.14 (1.06, 4.31)
Dockery et al. (1989) Study of respiratory symptoms in children in 6 cities in the U.S. Survey done 1980-1981	Daily monitoring of PM_{15}, sulfate fraction at each city	City PM_{15} means ranged from 20 to 59 µg/m^3	Cough, .02 to .09, Bronchitis .04 to .10, Lower resp. .07 to .16	Logistic regression	SO_2, NO_2, and ozone	Age, gender, maternal smoking	none	Cough 5.39 (1.00, 28.6) Bronchitis 3.26 (1.13, 10.28) Lower resp. 2.93 (0.75, 11.60)
Dockery et al. (1996) Study of children aged 8 to 12 in 24 communities in the U.S. and Canada.	PM_{10}, $PM_{2.1}$, sulfate, fine particle acidity	PM_{10} 26.3, range from 17.9 to 35.2 H^+ 27.5 nmoles/m^3, range from 0 to 51.9	Not given	Multiple logistic regression	SO_2, O_3, NH_4, HNO_2, HNO_3	Gender, history of severe chest illness, humidifier, environ. tobacco smoke, year of study		Bronchitis OR = 1.66 for range of particle strong acidity, OR = 1.65 (1.12, 24.2) for sulfate
Abbey et al. (1995a,b,c) Study of bronchitis, AOD, and asthma in Seventh Day Adventist adults	Daily monitoring of TSP, PM_{10} (visibility at 9 sites in no. and so. California)	Not given	AOD = 11.8% Bronchitis = 7.2%	Multi-logistic regression	SO_4, O_3, SO_2, NO_2	Age, gender, education, previous symptoms	none	1.23 AOD (0.91, 1.65) 1.39 Bronchitis (0.99, 1.92)

*Estimates calculated from data tables assuming a 50μg/m^3 increase in PM_{10} or 100 μg/m^3 increase in TSP.

All three studies suggest a chronic effect of PM on respiratory disease. The analysis of chronic cough, chest illness and bronchitis tended to be significantly positive for the earlier surveys described by Ware et al. (1986) and Dockery et al. (1989). Using a design similar to the earlier one, Dockery et al. (1996) expanded the analyses to include 24 communities in the United States and Canada. Bronchitis was found to be higher (odds ratio = 1.66) in the community with highest exposure of particle strong acidity when compared with the least polluted community. Fine particulate sulfate was also associated with higher reporting of bronchitis (OR = 1.65, 95% CI 1.12, 2.42).

The study of Abbey et al. (1995a,b,c) was done in California and showed results in the range of other studies. These studies suffer from the usual difficulty of cross sectional studies. Evaluation of PM effects is based on variations in exposure determined by a different number of locations. In the first two studies, there were six locations and in the third there were four. The results seen in all studies were consistent with a PM gradient, but it is impossible to separate out effects of PM and any other factors or pollutants which have the same gradient.

12.4.2.2 Pulmonary Function Studies

Studies of Children

Ware et al. (1986) studied lung function in children in early years of the Harvard Six Cities Study. A cross-sectional survey was done between 1974 and 1977. Lung function was measured at the time of the survey using a water filled recording spirometer. $FEV_{1.0}$ and FVC measurements were used in the analyses. Starting in 1978, dichotomous samplers were used to measure PM_{10}. Adjusted logarithms of the pulmonary function values were not related to TSP concentrations. The change in $FEV_{1.0}$ per $10\mu g/m^3$ change in TSP was .06% (.17%) at the first examination and -0.09% (.17%) at the second.

Dockery et al. (1989) also studied lung function in 10 to 12-year-old white children in the same six cities as noted above. Lung function was measured, using a water filled recording spirometer, at the time of a cross-sectional survey done in 1980 to 1981. The analysis was restricted to 5,422 children. In each community, a centrally located air monitoring station measured TSP, SO_2, NO_2, and O_3, starting in 1974; and dichotomous samplers were used to measure PM_{10} starting in 1978. Separate regressions of adjusted city-specific pulmonary function

levels on air pollution for children with and without asthma or wheeze did not show any associations.

Neas et al. (1994) analyzed a cohort of white children aged 7 to 11 from the same six cities for pulmonary function, using 1983 to 1988 data on: FVC; $FEV_{1.0}$; the ratio of $FEV_{1.0}$ to FVC; FEF_{25-75}; and the ratio of FEF_{25-75} to FVC. The regression model used the logarithm of the lung function value as the dependent variable and included gender, parental education, history of asthma, age, height, weight, and city as covariates. No statistically significant indoor $PM_{2.5}$ effects on lung function were found. The use of logarithms of the dependent variables, as well as the lack of overall mean lung function values, makes it impossible to directly compare the results of this study with those of others.

Stern et al. (1994) studied lung function and respiratory illness in five towns each in southwestern Ontario (Blenheim, Ridgetown, Tillsonburg, Strathroy, and Wallaceburg) and in south-central Saskatchewan (Esterhazy, Melville, Melfort, Weyburn, and Yorkton). Lung function measurements were made and self-administered parental questionnaires were given between October 1985 and March 1986. Pollution monitoring was not begun until late 1985, and included SO_2, NO_2, and O_3. PM_{10} was measured once every six days in the Ontario towns and every three days in the Saskatchewan towns. Lung function measurements included FVC, $FEV_{1.0}$, PEFR, FEF_{25-75}, and V_{50}max, and were adjusted for age, gender, weight, standing height, parental smoking, gas cooking, and standing height by gender interaction. Ontario children had statistically significant decrements in FCV (1.7%) and $FEV_{1.0}$ (1.3%) compared with Saskatchewan children, but no differences were found in the flow parameters. Actual exposure estimates for the individual towns were not used. The overall mean PM_{10} level in the Ontario towns was 23.0 $\mu g/m^3$ compared with 18.0 $\mu g/m^3$ for Saskatchewan.

Spektor et al. (1991) studied pulmonary function in children living in Cubatao, Brazil. PM_{10} and SO_2 measurements were made at six sites in Cubatao, located about 44 km from Sao Paulo. Average annual PM_{10} levels ranged from 43 to 140 $\mu g/m^3$. Pulmonary function measurements were made monthly from March to November, 1988. Individual regressions were performed using height, weight, and pollution as covariates, and average slopes were reported for each of six schools, but no confidence intervals were given. Both $FEV_{1.0}$ and PEFR were significantly related

to PM_{10} at the six schools. The average decrease in PEFR per 50 µg/m^3 was about 100 ml/sec, a value much larger than those seen in other studies.

During 1988, He et al. (1993) studied lung function in children in areas of Wuhan, China. The children (aged 7 to 13 years) were from six urban and one suburban school. Pollution measurements for TSP, SO_2, CO, and nitrogen oxides were collected by the Wuhan Environmental Protection Agency Air Pollution Monitoring Network from 1981 to 1988. All pollutants were higher at the urban site, with TSP values averaging 251 μg/m^3 as compared to 100 μg/m^3 at the suburban site. The cross sectional study was conducted in May and June of 1988. The hypothesis was that the relationship between lung function and height would be less in the urban city. Lung function growth curves were constructed by regressing $FEV_{1.0}$ and FVC on height for males and females for both areas. The curves were significantly steeper for the suburban children than for the urban children.

Arossa et al. (1987) studied lung function in approximately 2000 children in Turin, Italy, during a time period when both TSP and SO_2 were being reduced. Three areas of Turin (central city, peripheral area, and suburban area) were studied during the winters of 1980 to 1981 and 1982 to 1983. Each child's respiratory health was assessed at the beginning and end of the study using a questionnaire which also obtained demographic information. Lung function measurements included FVC, $FEV_{1.0}$, FEF_{25-75}, and MEF_{50}. Daily SO_2 and TSP measurements were available from seven monitoring sites in the area. The pollution data confirmed that the large SO_2 differences across areas in 1980 to 1981 were reduced substantially by 1982 to 1983. The differences in TSP remained small but constant during the time period. A general linear model analysis was used to calculated adjusted lung function values. From these values, individual slopes were estimated and these became the unit of analysis. Average slopes were significantly higher within the city of Turin when compared with the suburban area, suggesting to the authors that a decrease in pollution (primarily SO_2) resulted in an improvement of lung function.

Raizenne et al. (1996) studied pulmonary function test results from 22 North American communities chosen so that there was a gradient of acidic air pollution. Pollutants monitored included particulate acidity, total sulfate, $PM_{2.1}$, PM_{10}, SO_2, and O_3 (Spengler et al., 1996). Parents of children aged 8 to 12 years of age were surveyed between 1988 and 1990, and pulmonary function tests were administered in each community to coincide with the last two

weeks of the year-long air monitoring period. A two-stage regression analysis that adjusted for age, gender, weight, height, and gender-height interaction was used to relate the measurements of 10,251 white children to particulate pollution. A 52 nmole/m^3 difference in annual mean particle strong acidity was associated with a 3.5% deficit in adjusted FVC and a 3.1% deficit in adjusted FEV_1. The deficit was larger (but not statistically larger) in lifelong residents of their communities. Deficits were also found in PEFR and $FEF_{25-75\%}$. Ratios of FEV and FVC were not statistically significant. Slightly smaller deficits were seen using total sulfate, $PM_{2.1}$, and PM_{10} as pollutant exposure measures, with these deficits also being statistically significant, i.e. for FVC, SO_4^2 -3.06% (-4.5, -1.60); $PM_{2.1}$ -3.21% (-4.98, -1.41); PM_{10} -2.42 (-4.30, -0.51). The data did not allow for clear separation of effects of the various PM exposure indicators.

Studies of Adults

Chestnut et al. (1991) analyzed pulmonary function data from the NHANES survey conducted from 1971 to 1974 on the non-institutionalized U.S. population aged 1 to 74. The analysis was restricted to 49 urban sampling units where TSP measurements were available. A subsample of 6,913 adults (aged 25 to 74) were given spirometric tests using an Ohio Medical Instrument Corporation Model 800 electronic spirometer. Endpoints included FVC, $FEV_{1.0}$, and MMEF. The U.S. EPA's SAROAD data base was used to obtain data from population oriented air monitors in the 49 areas. Average TSP concentrations for previous years were used as the exposure measure. All individuals with reproducible results were included in a multiple regression analysis that included terms for age, height, gender, ethnic group, obesity, and TSP. Both a nonparametric analysis and a regression analysis suggested that TSP was associated with decreased FVC at TSP levels greater than 60 μg/m^3.

Tashkin et al. (1994) reported on the results of a long term lung function study of adults living in three areas of southern California. The areas were (1) Lancaster, with moderate levels of photochemical oxidants and low levels of other pollutants, (2) Glendora, with very high levels of photochemical oxidants, sulfates, and particulate matter, and (3) Long Beach, with high levels of sulfates and oxides of nitrogen. A mobile lung function laboratory was used to gather pulmonary function measurements and collect information on a modified NHLBI questionnaire. Residents of each area were tested twice over a 5 or 6-year interval, but during the same month each time.

The testing schedule was as follows: (1) Lancaster, 1973 to 1974 and 1978 to 1979; (2) Glendora, 1977 to 1978 and 1982 1983; and (3) Long Beach, 1974 1975 and 1980 to 1982. Significantly larger annual decreases in $FEV_{1.0}$ were found in both Long Beach and Glendora as compared with Lancaster. These results were consistent across gender, and were adjusted for age, height, smoking status, and allergies. The decrease was largest in Long Beach, but only slightly larger than in Glendora. Smoking showed a larger effect than did area of residence. No clear attribution of observed effects to one or the other of PM, NO_2, or photochemical oxidants was possible.

Ackermann-Liebrich et al. (1996) studied the effects of long term exposure to air pollutants on lung function in adults. A sample of 9651 subjects aged 18 to 60 were studied in eight different areas of Switzerland. FVC and FEV_1 were regressed against the natural logarithms of height, weight, age, age squared, gender, educational level, nationality, and work place exposure. Results were reported separately for never smokers and smokers. The results suggested that a 10 $\mu g/m^3$ increase in annual average PM_{10} was associated with a 3.4 percent decrease in FVC for healthy never smokers. Results were also consistent and significant for NO_2 and SO_2, but less so for O_3.

Xu et al. (1991) studied lung function in adults in areas of Beijing, China in 1986. A stratified sampling plan over three areas with historically different pollution was used. A trained interviewer obtained information on history of chest illness, respiratory symptoms, cigarette smoking, occupational exposure, residential history, educational level, and type of fuel used for cooking. Pulmonary function measurements were made according to guidelines of the American Thoracic Society. Outdoor particulate matter (TSP) and SO_2 were obtained for 1981 to 1985 from stations included in the World Health Organization Global Air Monitoring Programs. Multiple linear regression was used to assess the impact of air pollution on $FEV_{1.0}$ and FVC. Highly significant decreases in $FEV_{1.0}$ and FVC as a function of log(SO_2) and log(TSP) were found.

Chronic Pulmonary Function Studies Summary

The chronic pulmonary function studies (Table 12-22) are less numerous than the acute exposure studies. The Ware et al. (1986), Dockery et al. (1989), and Neas et al. (1994) studies

had good monitoring data and well-conducted standardized pulmonary function testing over many years, but showed no effect for children from particulate pollution indexed by TSP, PM_{15}, $PM_{2.5}$ or sulfates. On the other hand, Spektor et al. (1991) reported a decrease in PEFR in Brazilian children related to PM_{10} based on limited data from summer and winter of one year. Also, the latest study of Raizenne et al. (1996) found significant associations of effects on FEV_1 or FVC in U.S. and Canadian children with both acidic particles and other PM indicators. As for adults, Chestnut et al. (1991) reported that an increase in TSP was associated with a decline in FVC, and Ackermann-Liebrich et al. (1996) found a small but significant decrease in FVC related to PM_{10} in healthy adult non-smokers. Also, Xu et al. (1991) reported decrements in $FEV_{1.0}$ and FVC as a function of log (SO_2) and log (TSP). Overall, the available studies provide only very limited evidence suggestive of pulmonary lung function decrements being associated with chronic exposure to PM indexed by various measures (TSP, PM_{10}, sulfates, etc.). However, it should be noted that cross sectional studies require very large sample sizes to detect differences because the studies cannot eliminate person to person variation which is much larger than the within person variation. Thus, the lack of statistical significance cannot be taken as proof of no effect.

12.5 HUMAN HEALTH EFFECTS ASSOCIATED WITH ACID AEROSOL EXPOSURE

One key consideration in the evaluation of PM-health effects is: Are there specific chemical components of PM capable of being responsible for some or all of the noted associations between PM and human health? The presence of known toxic constituents within ambient particles would add to the plausibility of these associations. Since the time of the London Fog of 1952 and other major pollution episodes earlier in this century, the acidity of aerosols is one characteristic suspected of contributing to health effects by PM air

TABLE 12-22. STUDIES OF LONG-TERM PARTICULATE MATTER EFFECTS ON PULMONARY FUNCTION

Study	PM Type & No. Sites	PM Mean & Range	Model Type	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Ware et al. (1986) Study of lung function in children in 6 U.S. cities Survey done 1974-1977	Daily monitoring of TSP, SO_2, NO_2, and O_3 at each city	City TSP means ranged from 39 to 114 $\mu g/m^3$	Linear regression using logarithm of PFT value	SO_2, NO_2	City, gender, parental education, history of asthma, age, height, weight		Non-significant changes of .06% (-.27, .39) for first round and -.09% (-.42, .24) for second round
Dockery et al. (1989) Study of lung function in children in 6 cities in the U.S. Survey done 1980-1981	Daily monitoring of PM_{15}, sulfate fraction at each city	City PM_{15} means ranged from 20 to 59 $\mu g/m^3$	Linear regression using logarithm of PFT value	SO_2, NO_2	City, gender, parental education, history of asthma, age, height, weight		No significant relationship found with PM_{10}
Neas et al. (1994) Study of lung function in children in 6 cities in the U.S. Data collected from 1983-1988.	Daily monitoring of $PM_{2.5}$ and sulfate fraction at each city	Not given	Linear regression using logarithm of PFT value	SO_2, NO_2, and O_3	City, gender, parental education, history of asthma, age, height, weight	$PM_{2.5}$	FVC and FEV_1 not changed. Values could not be converted to mls.
Raizenne et al. (1996) Study of lung function in children aged 8 to 12 in 22 communities in the U.S. and Canada.	24 hour samples of particle strong acidity at 22 sites, as well as $PM_{2.1}$, PM_{10}, and sulfates	Not given	Two step linear regression using natural logarithm of lung function	ozone	Age, weight, height, gender, and gender by height interaction	All PM measures separately	Decreases in FVC and FEV_1 were about 2 to 3.5 percent over the range of the pollution measures.

TABLE 12-22 (cont'd). STUDIES OF LONG-TERM PARTICULATE MATTER EFFECTS ON PULMONARY FUNCTION

Study	PM Type & No. Sites	PM Mean & Range	Model type	Other pollutants measured	Weather & Other Factors	Pollutants in model	Decrease* (Confidence Interval)
Spector et al. (1991) Study of lung function in school-age children in Cubatao, Brazil. Lung function measured in the summer and winter of 1988.	12 hour samples of PM_2 and PM_{10} were collected at 6 sites from March to November, 1988.	PM_{10} ave. annual means ranged from 43 to 140 $\mu g/m^3$	Linear regression using previous months ave. PM_{10} at the local site	SO_2 and ozone	not given	PM_{10}	Decreases in FEV_1 averaged about 2.5 mL/($\mu g/m^3$) per 50 $\mu g/m^3$ PM_{10}.
Ackermann-Liebrich et al. (1996), study of 9,651 adults in 8 areas of Switzerland done in 1991	Continuous measurements of SO_2, NO_2, TSP, O_3, and PM_{10}	PM_{10} in 1993 ranged from 10.1 to 33.4; mean 21.2	Linear regression using logarithm of PFT value	TSP, SO_2, NO_2, O_3	Height, weight, age, gender, atopic status		Significant 3.4% decrease in FVC and 1.6% FEV1 decrease related to PM_{10} in healthy non-smokers. Similar results found for non- and former smokers.

*Decreases in lung function calculated from parameters given by author assuming a 50 $\mu g/m^3$ increase in PM_{10} or 100 $\mu g/m^3$ increase in TSP.

pollution. Though certainly not the only PM component with potentially toxic effects, acidic aerosols have received more epidemiologic study than have other PM components, to date.

Several epidemiologic studies have directly examined the health effects associated with ambient particulate strong acid aerosol (H^+) exposures. The historical scarcity of such analyses was due in large part to the absence of adequate ambient acid measurement techniques in the past and to the lack of routine acid aerosol monitoring in more recent years. However, studies now exist that allow an assessment as to whether human health effects may be associated with exposures to ambient acid aerosols, both: (1) as derived from reexamination of older, historically important data on air pollution episode events in North America and Europe, and; (2) as can be deduced from more recent epidemiology studies carried out in the U.S., Canada, and Europe. This section concisely reviews these studies, first as they relate to acute exposure effects, and then as they pertain to chronic exposure effects. Because of the relative scarcity of direct acid aerosol measurements until recent years, part of this section is also devoted to identifying studies of situations in which there is good reason to suspect that high ambient acid concentrations existed in the evaluated study areas. From all of these studies, the nature of any observed health associations are summarized as a basis for drawing health effects conclusions, and for suggesting directions for future research. The material in this review was based upon the acid aerosols issue paper prepared by the U.S. Environmental Protection Agency (1989), as well as more recent evidence, as appropriate.

12.5.1 Evidence Evaluating the Relationship between Acid Aerosols and Health Effects During Pollution Episodes

Some of the earliest indications of associations between ambient air acid aerosols and human health effects can be discerned upon reexamination of historically important air pollution episode events. These include, for example, the Meuse Valley (Belgium), Donora, PA (USA), and well-known London (UK) episodes, as discussed below.

12.5.1.1 Meuse Valley

Firket (1931) described morbidity and mortality related to the fogs of December 1930 in the Meuse Valley of Belgium. A detailed discussion of health effects causes was presented, and he concluded that, while multiple pollutants existed in this atmosphere, the main component of the fog that caused the observed health effects was sulfuric acid. This conclusion was based both upon consideration of the emissions in the valley, the weather conditions and the aerometric chemistry required for the production of sulfuric acid. Additionally, the pathophysiology seen was thought to relate to sulfuric acid exposure more so than to other possible agents. More than 60 persons died from this acid fog and several hundred suffered respiratory problems, with a large number becoming complicated with cardiovascular insufficiency. The mortality rate during the fog was over ten times higher than the normal rate. Those persons especially affected by the fog were the elderly, those suffering from asthma, heart patients, and other debilitated individuals. Most children were not allowed outside during the fog and few attended school. Unfortunately, no actual measurements of acid aerosols in ambient air during the episode are available by which to establish clearly their role in producing the observed health effects versus the relative contributions of other specific pollutants.

12.5.1.2 Donora

Schrenk et al. (1949) reported on atmospheric pollutant exposures and the health effects of the smog episode of October 1948 in Donora, PA. A total of 5,910 persons (or 42.7 percent) of the total population of Donora experienced some effect from the smog. The air pollutant-laden fog lasted from the 28th to the 30th of October, and during a 2-week period 20 deaths took place, 18 of them being attributed to the fog. An extensive investigation by the U.S. Public Health Service concluded that the health effects observed were mainly due to an irritation of the respiratory tract. Mild upper respiratory tract symptoms were evenly distributed through all age groups and, on the average, were of less than four days duration. Cough was the most predominant symptom; it occurred in one-third of the population, and was evenly distributed through all age groups. Dyspnea was the most frequent symptom in the more severely affected, being reported by 13 percent of the population, with a steep rise as age progressed to 55 years; above this age, more than half of the persons affected complained of dyspnea.

It seems reasonable to state that, while no single substance can be clearly identified as being responsible for the October 1948 episode, the observed health effects syndrome could have likely been produced by two or more of the contaminants, i.e., SO_2 and its transformation products together with other PM constitutes, as among the more significant contaminants present. Hemeon (1955) examined the water soluble fraction of solids on a filter of an electronic air cleaner operating during the smog in Donora and concluded that acid salts were an important component.

12.5.1.3 London Acid Aerosol Fogs

Based on the mortality rate in the Meuse Valley, Firket (1931) had estimated that 3,179 sudden deaths would likely occur if a pollutant fog similar to that in the Meuse Valley occurred in London. An estimated 4,000 deaths did later indeed occur during the London Fog of December 1952, as noted by Martin (1964). During that fog evidence of bronchial irritation, dyspnea, bronchospasm and, in some cases, cyanosis is clear from hospital records and from the reports of general practitioners. There was a considerable increase in sudden deaths from respiratory and cardiovascular conditions. The nature of these sudden deaths remains a matter for speculation since no specific cause was found at autopsy. Evidence of irritation of the respiratory tract was, however, frequently found and it is not unreasonable to suppose that acute anoxia due either to bronchospasm or exudate in the respiratory tract was an important factor. Also, the United Kingdom Ministry of Health (1954) report on this fog stated that, in the presence of moisture, aided perhaps by the surface activity of minute solid particles in fog, some sulfur dioxide is oxidized to trioxide. The report concluded that: "It is probable, therefore, that sulfur trioxide dissolved as sulfuric acid in fog droplets, appreciably reinforced the harmful effects."

Martin and Bradley (1960) reported increases in daily total mortality among the elderly and persons with preexisting respiratory or cardiac disease in relation to SO_2 and PM (measured as British Smoke; BS) levels in London during fog episodes in the winter of 1958 to 1959. The pathological findings in 12 fatal cases and the clinical evidence of practitioners seem to indicate clearly that the harmful effects of the fog were produced by the irritating action of polluted air drawn into the lungs. These effects were more obvious in people who already suffered from a chronic respiratory disease and whose bronchi were presumably more liable to bronchospasm.

Waller (1963) reported that sulfuric acid was one of the pollutants considered as a possible cause of the increased morbidity and mortality noted during the London fog of December 1952. As noted earlier, following the 1952 pollution episode daily measurements of BS and SO_2 made in London starting in 1954. Concentrations of sulfuric acid, calculated from net aerosol acidity, were also measured during air pollution episodes and, later, on a daily basis, starting in 1963. All of these historical acid measurements must be viewed with caution, since filter artifact formation is possible for these samples. For example, there was no attempt to protect the sample filters from ambient SO_2 or NH_3, which could result in excess acid formation or in acid neutralization, respectively, on the samples. No regular measurements of sulfuric acid were made during the winter of 1955 to 1956, but some was detected at times of high pollution. For example, Waller and Lawther (1957) detected the presence of acid droplets in samples collected in January of 1956. Insufficient measurements were made, however, during the rest of the winter of 1955 to 1956 to study the effects of the acid aerosol present. Waller (1963) later reported measuring acid droplets in London in the winter of 1958 to 1959 with mass median diameter of 0.5 μm. Commins (1963) measured particulate acid in the city of London and found concentrations especially high at times of fog reaching H^+ levels of 678 $\mu g/m^3$ of air (calculated as sulfuric acid). Typical winter daily concentrations were 18 $\mu g/m^3$ compared to 7 $\mu g/m^3$ in the summer. The sulfuric acid content of the air in the city of London at the time could range up to 10 percent of the total sulfur.

Acid aerosol data collected by Commins and Waller (1967) during the December 1962 London Fog episode, which occurred almost exactly 10 years after the 1952 episode, provide some of the strongest evidence that acid aerosols were elevated during the 1950's episodes. As shown in Figure 12-10, 24 h average acid concentrations reached 378 $\mu g/m^3$ (as H_2SO_4) on the peak mortality day during this later, less severe, London episode. Both BS and SO_2 were similarly elevated on these episode days, however, so it is not possible to identify

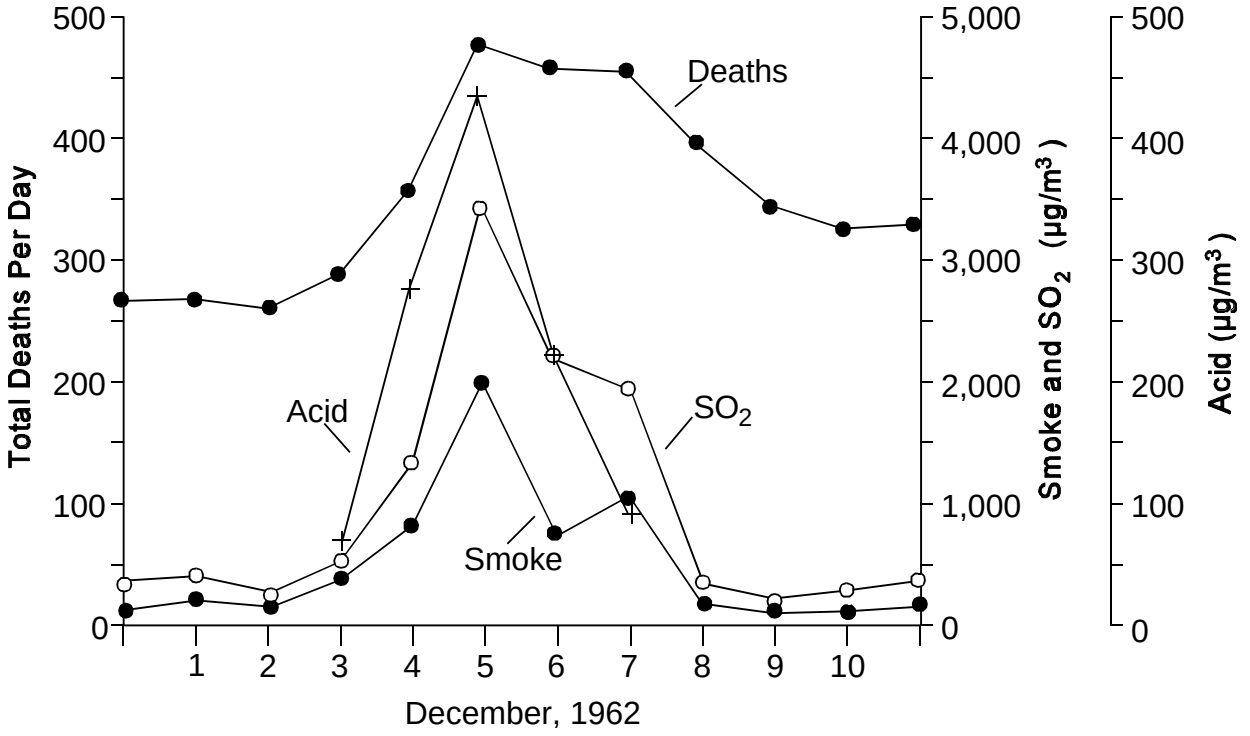

Figure 12-10. December 1962, London pollution episode.

Source: Adapted from Ito (1990).

H_2SO_4 as the sole causal pollutant. Not all of the measured acids during fog episodes would necessarily be respirable, reducing their health effects from that implied by the total H_2SO_4 concentration. However, these H^+ data from the 1962 episode do support past anecdotal evidence that elevated strong acid concentrations were present during the major London Fog pollution episodes.

Lawther et al. (1970) reported an association between daily pollutant levels (BS and SO_2) and worsening of health status among a group of over 1,000 chronic bronchitis patients in London during the winters of 1959 to 1960 and 1964 to 1965. A daily technique for self-assessment of day-to-day change in health status was used. The concentration of acid aerosol rose with that of smoke, and it is likely to have been partly responsible for health effects observed in these chronic bronchitic patients. Since many patients' symptoms become worse even at times of relatively low humidity, this suggests that small droplets of strong acid had more effect than larger ones. An

interesting study was also conducted on a smaller sample of the patients during in the winters of 1964 to 1965 and 1967 to 1968 when pollutant levels were somewhat lower than in earlier years. Approximately 50 subjects selected for their susceptibility to air pollutant effects formed the cohort. Daily apparent sulfuric acid, measured at St. Bartholomew Hospital Medical College, was reported as having a relatively high correlation with health effects in the 1964 to 1965 winter. For 1967 to 1968, all these correlation coefficients were lower, but still significant. The authors comment that the patients selected must have been particularly sensitive to pollution, since from past experience no correlation would have been expected with such very low levels of pollution encountered by such a small group.

The studies discussed above suggest that mortality and morbidity effects can be associated with pollutant mixes which included elevated levels of ambient air concentrations of acid aerosols. The calculations and measurements of sulfuric acid levels (estimated to range up to 378 (24-h) or 678 $\mu g/m^3$ (1-h) during some London episodes in the late fifties and early sixties provide a plausible basis for hypothesizing contributions of sulfuric acid aerosols to the health effects observed during those episodes.

12.5.2 Quantitative Analysis of Earlier Acid Aerosol Studies

12.5.2.1 London Acute Mortality and Daily Acid Aerosol Measurements

Thurston et al. (1989) conducted a reanalysis of the London mortality data for a multi-year period in which daily direct acid aerosol measurements were made at St. Bartholomew's Medical College. The data considered in this analysis include pollution and mortality records collected in Greater London during winter periods (November 1 to February 29) beginning in November 1963 and ending in February 1972. The air pollution data were compiled from one of two sources. First, BS and SO_2 data (as reported in $\mu g/m^3$) were compiled as daily means of seven sites run by the London County Council and spatially distributed throughout London County. A second data set of BS, SO_2 and aerosol acidity (calculated as $\mu g/m^3$ sulfuric acid) was also compiled for one central London site run by the Medical Research Council Air Pollution Research unit at the St. Bartholomew's Medical College. The Greater London mortality data were obtained from the London General Register Office for winter periods (November to February) beginning in 1958, and for all days commencing in April 1965. Total mortality, respiratory mortality, and

cardiovascular mortality were all compiled daily during these periods, but only total mortality was considered in this work. The Greater London population was fairly stable during the period considered in this research (1963 to 1972), averaging about 8 million people. The pollution and mortality data for each of the nine winters of data were combined into one data set for analysis. This is reasonable in this case because the period under study, late 1963 to early 1972, is subsequent to the implementation of the London smoke control zones (1961 to 1963), and is therefore a period of fairly constant average winter pollutant concentrations. Prior to combining the data, each year's total mortality data were also prefiltered using a high-pass filter that weights the mortality data in a manner very similar to the calculation of deviations from a 15-day moving average of mortality, except that it eliminates the undesirable long-term cyclical fluctuations. Although the filtered total mortality has largely removed slow moving fluctuations in the mortality data, the winters of 1967 to 1968 and 1969 to 1970 were still slightly nonstationary, probably due to influenza epidemics in those years. It may have been desirable to also control for these remaining effects by considering an influenza epidemic dummy variable in subsequent regression analyses of these data. The resulting data set comprised a total of 921 observations of daily pollution, total mortality, and filtered total mortality data for the nine-winter data set.

In the Thurston et al. (1989) results, the log of H_2SO_4 measured at the central site was much more strongly correlated with raw total daily mortality than any measure of BS or SO_2 especially when it was correlated with the next day mortality ($r = 0.31$). It is also clear that the logarithm transformation enhances the acid-mortality association more than is true for BS or SO_2. For the filtered mortality variable, however, the H_2SO_4 correlation with next day filtered mortality (e.g., $r = 0.19$ for log (H_2SO_4) was weakened versus that for raw total mortality. Thus, the St. Bartholomew's College H_2SO_4 measurements appear to be correlated with Greater London mortality, especially before the mortality data are filtered for slow moving fluctuations. Mortality-pollution crosscorrelation analyses indicated that mortality effects usually followed pollution in time even after filtering both series (Thurston et al., 1989), a basic consideration in inferring casual association.

The superiority of the log of H_2SO_4 concentration versus the raw H_2SO_4 data in correlations with total mortality agrees with the previous analyses of British Smoke-total mortality associations. This may imply that a "saturation" of mortality effects is indeed occurring over two

or more days, and that a cumulative effect of several episode days may be more relevant than modeling a single day effect alone. This may be due to avertive behavior, especially since episode warnings were publicized at the time of high pollution. Most likely, however, the "saturation" of effects is due to the premature death of the most susceptible people on prior moderate pollution days.

A more extensive analysis of the London total mortality and acid aerosol data was conducted by Ito et al. (1993) for 1965 to 1972, when daily acid measurements were available year-round and the air pollution levels were non-episodic (see Figure 12-11). BS, SO_2, H_2SO_4, and weather variables (temperature and humidity) were examined for their short-term associations with daily mortality after removal of long-term components from each series via prewhitening, in order to obtain "rational" crosscorrelations. Power spectra of the variance of mortality, pollution, and temperature variables were employed in the development of this model. Also, first order autocorrelations were found to be significant, and were evaluated. Significant associations with same day and following days' mortality were found for all three pollutants considered. In the most extensively controlled model, the winter mean pollutant effect was estimated to range from 2 to 3% of the mean 278 deaths/day total mortality, but all three pollutants gave similar results (for mean H_2SO_4 = 5.0 $\mu g/m^3$, SO_2 = 293 $\mu g/m^3$, or BS = 72 $\mu g/m^3$) and their respective effects could not be separated, due to their high intercorrelation. These models were fit to the (separate) 1962 London acid/mortality episode data and found to fit well, supporting the validity of such deviation-derived mortality estimates.

Lippmann and Ito (1995) conducted a preliminary graphically-based analysis of the year-round 1965 to 1972 London pollution and mortality data set that controlled for same-day temperature effects by analyzing restricted temperature ranges in each season. This was done to provide an alternative to more empirical approaches applied to these data in prior analyses. In each season, the majority of days fell within one or two temperature ranges, within which the mortality also fell within narrow ranges. Within these restricted ranges,

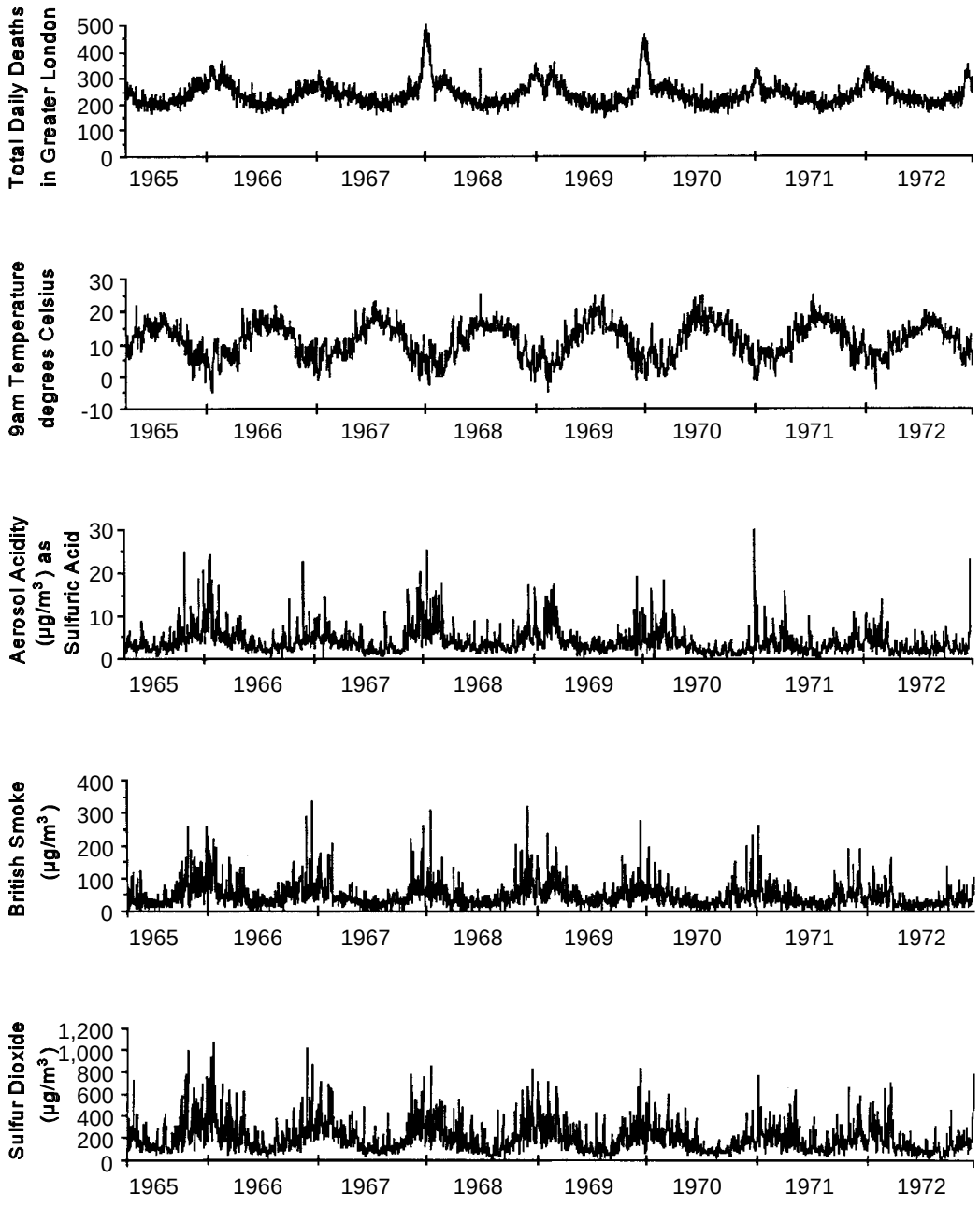

Figure 12-11. Time series plots of daily mortality, pollution, and temperature in London, England, 1965 to 1972 (Ito et al., 1993).

analyses indicated that there were relatively strong associations between daily mortality and the daily logs of the concentrations of H^+ and SO_2. By contrast, the mortality association with BS was much weaker, especially in the winter and summer. The authors indicate that more comprehensive analyses are needed, but assert that such analyses provide a useful complement to model-based approaches. Things as yet not addressed by this analysis include the need to control for the potential effects of prior days' extreme temperatures (i.e., lagged effects), which are known to be important in winter, and the direct addressing of potential temperature effects within the ranges considered. Probably the most interesting result of these analyses is that the H^+-mortality association is found even in the summertime, when the daily H^+ concentrations do not exceed approximately 10 $\mu g/m^3$, as H_2SO_4 (~ 200 nmoles H^+/ m^3), which are concentrations not unlike those presently experienced during the summer in the eastern United States.

These recent analyses by Thurston et al. (1989) and by Ito et al. (1993) of daily direct acid aerosol measurements over a long span of time (1963 to 1972) in London are especially important in providing more data to examine for associations between acute exposures to ambient acid aerosols and mortality at H^+ levels more relevant to those presently seen in North America. Also, the work of Lippmann and Ito (1995) indicates that this acute H^+-mortality association can exist at concentrations below 200 nmoles/m^3 H^+, and under summertime conditions.

12.5.3 Studies Relating Acute Health Effects to Sulfates

Sulfate species usually represent the principal component of particulate strong acid aerosols (primarily as H_2SO_4 or NH_4HSO_4). As a result, variations in measured sulfate levels have been found to represent a reasonably reliable surrogate for variations in strong particulate acid aerosol levels over time at a site (Lippmann and Thurston, 1995). However, sulfates are not necessarily as useful for intercomparing aerosol particulate acidity levels between sites. This is because measurements of total sulfate levels comprise not only strongly acidic sulfates, but, in fact, are usually dominated by sulfates that are only weakly acidic (e.g., $(NH_4)_2SO_4$). Moreover, it has been found that local ammonia levels can diminish the ambient $H^+/SO_4^=$ ratio experienced at a site by neutralizing the strongly acidic sulfates (Suh et al., 1995). For this reason, two sites located in differing environs (e.g., urban versus suburban) may have similar $SO_4^=$ levels but different $H^+/SO_4^=$ ratios, merely because the population density around the two sites is different (Ozkaynak et al.,

1994). Therefore, cross-sectional studies using sulfates may be limited in the insight they may provide into the potential health effects of acid aerosol exposures, especially if they compare sites with differing surrounding land uses. However, if two monitoring sites are in the same airshed, they will usually still be highly correlated over time, as their particulate H^+ concentrations will rise and fall together from day to day as regional sulfate levels rise and fall (e.g., see Thurston et al. 1994a). The surrounding land use dependence of the $H^+/SO_4^=$ ratio may limit somewhat the usefulness of sulfates as an index of H^+ differences between sites but may not adversely affect time series studies using sulfate data as an index of particulate aerosol strong acidity.

12.5.3.1 Canadian Hospital Admissions Related to Sulfate Acute Exposure Studies

Bates and Sizto (1983, 1986) reported results of an ongoing correlational study relating hospital admissions in southern Ontario to air pollutant levels. Data for 1974, 1976, 1977, and 1978 were discussed in the 1983 paper. The 1986 analyses evaluated data up to 1982 and showed: (1) no relationship between respiratory admissions and SO_2 or COH in the winter; (2) a complex relationship between asthma admissions and temperature in the winter; and (3) a consistent relationship between respiratory (both asthma and non-asthma) admissions in summer and sulfate and ozone concentrations, but not to summer COH levels. However, Bates and Sizto noted that the data analyses were complicated by long-term trends in respiratory disease admissions unlikely related to air pollution. They nevertheless hypothesized that observed effects may be due to a mixture of oxidant and reducing pollutants which produce intensely irritating gases or aerosols in the summer, but not in the winter.

Bates and Sizto (1987) later studied admissions to all 79 acute-care hospitals in Southern Ontario, Canada (i.e., the whole catchment area of 5.9 million people) for the months of January, February, July and August for 1974 and for 1976 to 1983. Means of the hourly maxima for O_3, NO_3, SO_2, coefficient of haze (COH), and aerosol sulfates were obtained from 17 stations between Windsor and Peterborough. Sulfates were measured every sixth day. Total admissions and total respiratory admissions declined about 15 percent over the course of the study period, but asthma admissions appeared to have risen. Evaluating the asthma category of admissions is complicated by the effects of a change in International Classification of Disease (ICD) coding in 1979. The analyses demonstrated that there was a consistent summertime relationship between

respiratory admissions (with or without asthma) and sulfates, ozone, and temperature. This conclusion was strengthened by the continuing lack of any association of these variables with non-respiratory conditions. The 1987 paper raised the question of whether the association of increased respiratory admissions in the summer in this region could be associated with ozone or sulfates. It was aerosol sulfates that, in summertime, explained the highest percentage of the variance in respiratory admissions; yet these were not correlated with respiratory admissions in the winter. In view of this, the authors hypothesized that the observed health effects might be attributable neither to ozone nor to sulfates, but to some other air pollutant species that "travel" with them over the region in the summer (but not in the winter).

Bates and Sizto (1987) noted that recent observations suggested the presence of peaks of H^+ aerosol of small particle size in this region of Canada in the summer, concomitant with elevated O_3 and $SO_4^=$ levels. On two days in July 1986 in eastern Toronto when ozone and sulfate levels were elevated, but not higher than on other days, peaks of H^+ acid aerosol lasting for up to 2 h were recorded at levels of 10 to 15 $\mu g/m^3$. The particle size was small (about 0.2 µm). Similar observations were recorded on the same days by another H^+ air sample operation southwest of Toronto. They raised the possibility that the types of health effects noted above might be attributable neither to ozone, nor to sulfates, but rather perhaps to acid aerosols. Thus, the evidence from Bates and Sizto (1983, 1986, 1987, 1989) neither conclusively relates sulfates nor ozone to hospital admissions. Instead, the authors conclude that the results suggest that some other pollutant(s) may be responsible, i.e., the strongly acidic summer haze that has since been measured in the region.

Lipfert and Hammerstrom (1992) reanalyzed the Bates and Sizto (1989) hospital admissions dataset for 79 acute-care hospitals in southern Ontario, incorporating more elaborate statistical methods and extending the dataset through 1985. Pollutants considered included SO_2, NO_2, O_3, $SO_4^=$, COH, and TSP. Long-wave influences were reduced by using the short study periods previously employed by Bates and Sizto (e.g., July and August only for summer), as well as by employing very conservative prewhitening procedures to the data. Day of week effects were also controlled. In addition, the models were more extensively specified, including a variety of new meteorological variables such as wind speed (correlated at r=-0.5 with COH). Despite this possible model overspecification, however, summerhaze pollutants (i.e., O_3, $SO_4^=$, and SO_2) were

found to have significant associations with hospital admissions in southern Ontario. In contrast, pollution associations with hospital admissions for accidental causes were nonsignificant in these models. While air pollution concentrations were generally within U.S. standards, the pollutant mean effect accounted for 19 to 24% of all summer respiratory admissions (mean admissions 40/day, mean $SO_4^=$ 11 µg/m^3), although the "responsible" summertime haze pollutant(s) could not be discerned by the authors with certainty.

Burnett et al. (1994) related the number of emergency or urgent daily respiratory admissions at 168 acute care hospitals in all of Ontario during 1983 to 1988 to estimates of ozone and sulfates in the vicinity of each hospital. No other pollutants were directly considered in this analysis, although the authors reported that SO_2 and NO_2 were only weakly correlated with SO_4 in these data (r 0.3), so these pollutants were unlikely to be confounders. Daily levels of sulfates were recorded at nine monitoring stations located throughout the province. Long-wave cycles in the admissions data were removed using a 19-day moving average equivalent high pass filter. A random effects model (wherein hospital effects were assumed to be random) was employed, using the generalized estimating equations (GEE) of Liang and Zeger (1986). After adjusting admissions data for seasonal patterns, day of week effects, and individual hospital effects, positive and statistically significant associations were found between hospital admissions and both ozone and sulfates lagged 0 to 3 days. Positive associations were found in all age groups (0 to 1, 2 to 34, 35 to 64, 65+). The bivariate relationship found between adjusted admissions and sulfates in these data are shown in Figure 12-12. In simultaneous regressions, five percent of daily respiratory admissions in the province during May to August (mean = 107.5/day) were found to be associated with O_3 (at 50 ppb), and one percent with $SO_4^=$ (at 5 µg/m^3). Positive

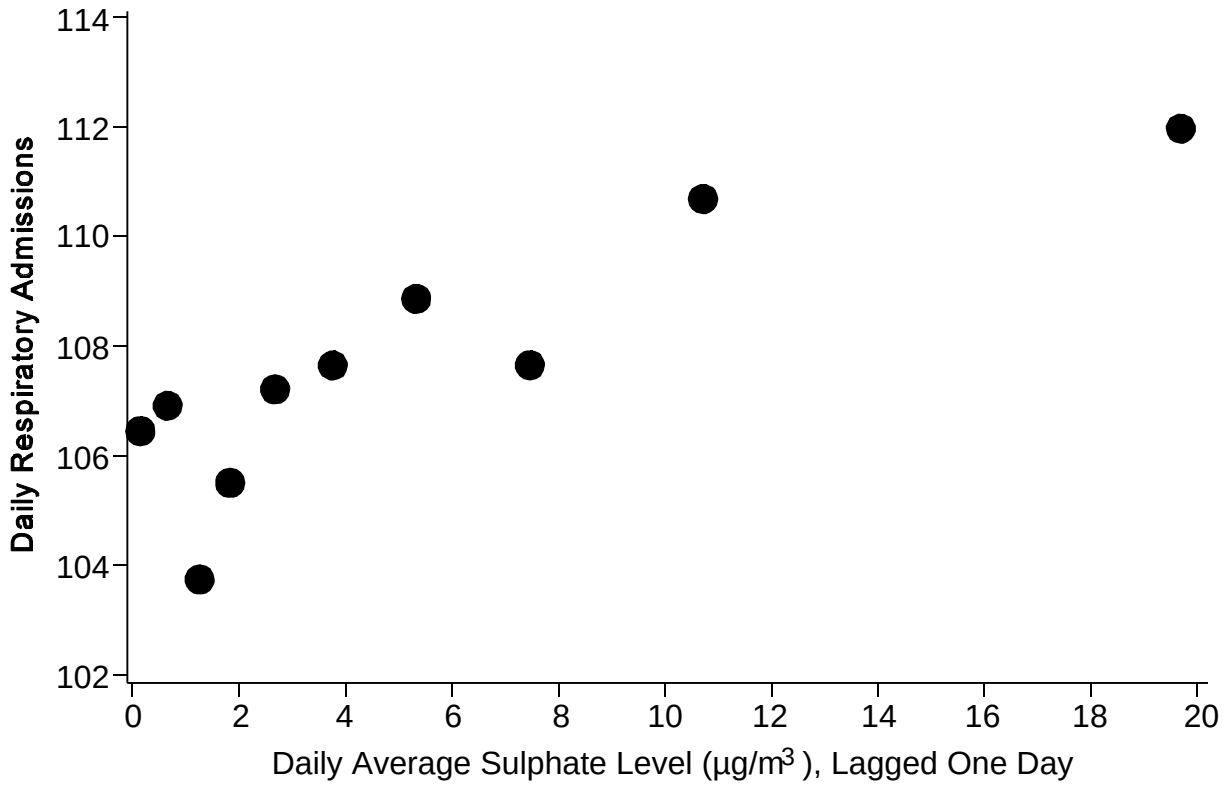

Figure 12-12. Average number of adjusted respiratory admissions among all 168 hospitals by decile of the daily average sulfate level (μg/m^3), 1 day lag.

Source: Burnett et al. (1994).

and significant air pollution associations were found for asthma, chronic obstructive pulmonary disease (COPD), and infections, but not for nonrespiratory (control) admissions, nor for respiratory admissions in the winter months (when people are indoors and levels of these pollutants are low). While these analyses employed much more sophisticated statistical methods, the results generally consistent with Bates and Sizto's prior work in this region, though ozone was found to yield a larger effect than sulfates in this study. The authors point out that $PM_{2.5}$ and H^+ are highly intercorrelated with sulfates in the summer months ($r > 0.8$), and that one of these agents may be responsible for the health effects relationships found with sulfates in this work. In Burnett et al. (1995), sulfate was also a predictor of hospital admissions for both respiratory and cardiac admissions, as discussed in Section 12.3.2.

12.5.3.2 Other Health Effects Related to Sulfate Exposures

Ostro (1987) conducted a cross-sectional analysis of the U.S. Inhalable Particle Monitoring Network airborne particulate matter dataset, but analyzed the 1979 to 1981 annual Health Interview Surveys (HIS) to test if there were acute morbidity associations coherent with those found for mortality by Ozkaynak and Thurston (1987) during this period. Ostro reported a stronger association between several measures of morbidity (work loss days, restricted activity days, etc.) and lagged fine particle estimates than found with prior 2-week average TSP levels in 84 U.S. cities. In this analysis, a Poisson model was employed, due to the large number of zeros in the dependent variables (i.e., days with morbidity), and the analyses focused on adults aged 18 to 65. Smoking was not considered in the model, since not all metropolitan areas had data and the correlation between smoking and any of the pollutants was less than 0.03 and non-significant in the one-third of the HIS sample for which smoking data were available. This suggests that, while presumably generally important to morbidity, smoking was not a likely confounder to air pollutants in these cross-sectional analyses. Ostro concluded that his findings were consistent with the results of prior cross-sectional analyses reporting an association between mortality and exposures to fine particles and sulfates, and that "to the extent that sulfuric acid aerosols are correlated with sulfates, the results suggest that respiratory morbidity may be related to atmospheric acidity."

12.5.3.3 Studies Relating Acute Health Effects to Acidic Aerosols

In recent years, a number of new studies have been conducted of acute health effects employing direct measurements of particulate strong acid aerosols. These allow a more direct test of the hypothesis that it is the H^+ that is responsible for the sulfates-health effects associations noted in past work.

12.5.3.4 Acute Acidic Aerosol Exposure Studies of Children

Several studies have recently been carried out in the United States and Canada that examine the effects of exposures to air pollutants on pulmonary function in children at summer camps. Some of the available data derived from these studies allow evaluation of the possible involvement

of acid aerosols in the health effects observed. Furthermore, recent children's diary studies have also investigated acid aerosol effects on respiratory symptoms in the general population.

Studies of Pulmonary Function in Children at Summer Camp

Lippmann et al. (1983) studied 83 nonsmoking, middle class, healthy children (ages 8 to 13) during a 1980 2-week summer camp program in Indiana, PA. The children were involved in camp activities which resulted in their exercising outdoors most of the time. At least once, each child had height and weight measured and performed spirometry on an 8 liter Collins portable recording spirometer in the standing position without nose clip. During the study, peak flow rates were obtained by Mini-Wright peak flow meter at the beginning of the day or at lunch and adjusted for both age and height. Ambient air levels of TSP, hydrogen ions, and sulfates were monitored by a high-volume sampler on the rooftop of the day camp building. Ozone levels were estimated using a model that used ozone data from monitoring sites located 32 and 100 km away. The hi-volume samples were collected on H_2SO_4 treated quartz fiber filters for the determination of the concentration of H^+ and total suspended particulate matter (TSP). H^+ was determined from filter extract using a Gran titration. Peaks in acid concentration occurred on four days, when the acid values ranged between 4 and 6.3 $\mu g/m^3$ (if as H_2SO_4). On many occasions, there was no measurable H_2SO_4 in the atmosphere. While effects were reported as being significantly associated with exposure to ozone, no effects were found to be related to exposure to H_2SO_4 at the relatively low levels observed during the study.

Bock et al. (1985) and Lioy et al. (1985) examined pulmonary function of 39 children at a camp in Mendham, New Jersey during a 5-week period in July to August, 1982. Ozone was continuously monitored using chemiluminescent analysis. Ambient aerosol samples were collected on Teflon filters with a dichotomous sampler having a 15 µm fractionation inlet and a coarse/fine cut size of 2.5 µm (Sierra Model 244-E). Aerosol acidity as measured by strong acid (H^+) content, was determined using the pH method. Highly significant changes in peak expiratory flow rate (PEFR) were found to be related to ozone exposure, as well as a baseline shift in PEFR lasting approximately one week following a haze episode in which the O_3 exposure exceeded the NAAQS for four consecutive days that included a maximum concentration of 185 ppb. There was no apparent effect of H^+ on pulmonary function. The authors did state, however, that the

persistent effects associated with the ozone episode could have been due to acid sulfates as well as, or in addition to, ozone, but additional uncollected data were needed to evaluate this possibility.

During a 4-week period in 1984, Lioy et al. (1987) and Spektor et al. (1988) measured respiratory function of 91 active children who were residing at a summer camp on Fairview Lake in northwestern New Jersey. Continuous data were collected for ambient temperature, humidity, wind speed and direction, and concentrations of O_3, H_2SO_4, and total sulfates were determined. Ozone was measured by U.V. absorption, and H_2SO_4 and total sulfates were alternately determined by a flame photometric sulfate analyzer (Meloy Model 285) preceded by a programmed thermal pretreatment unit. The ambient aerosol samples were collected on quartz fiber filters with a dichotomous sampler having a 15 μm fractionating inlet (PM_{l5} and a coarse/fine cut-size of 2.5 μm (Sierra Model 244-E). Aerosol acidity, as measured by strong acid (H^+) content, was determined using the pH method. The maximum values recorded for H_2SO_4 and NH_4HSO_4 were 4 and 20 μg/m^3 respectively. While effects were reported as being associated with exposure to ozone, no effects were found to be directly related to exposure to the acid aerosol concentrations experienced in this study.

Raizenne et al. (1987) reported analyses of data from a study in Ontario, Canada. In 1983, fifty two campers (23 were asthmatics) at a summer camp were studied to examine lung function performance in relation to daily pollutant concentrations. The health assessment included a pre-camp clinical evaluation, a telephone administered questionnaire on respiratory health, daily spirometry and symptoms measurements. Pollutants measured included O_3, respirable particles, sulfates, NO_2, and SO_2. Respirable sulfates were highly variable and ranged from 10 to 26 μg/m^3. Sulfate as sulfuric acid was usually very low. Raizenne et al. (1989) report that O_3, sulfate, and $PM_{2.5}$ were associated with decrements in lung function of children. Evidence of decrements in specific lung function indices were related to current pollution levels and to a 12 to 24 h lag function for $PM_{2.5}$, SO_4, O_3 and temperature. Although both asthmatic and non-asthmatics had similar data trends, only responses in the non-asthmatic group reached statistical significance. The authors note that all of the air pollutants were highly correlated, and thus it was not possible to apportion health effects to the individual pollutants.

Raizenne et al. (1989) studied 112 young girls who participated in one of three 2-week camp sessions at camp Kiawa, Ontario, Canada during June to August, 1986. They examined the subjects in relation to four ambient acid aerosol events (the highest H_2SO_4 level was 47.7 $\mu g/m^3$ during one event on July 25, 1986). The influence of air pollution on lung function was evaluated first by comparing responses on the day of a pollutant event (high acid and ozone levels) to the mean of the responses on corresponding days of low pollutant levels. For $FEV_{1.0}$ there was tendency for the lung function decrements on the event day to be greater than the response on the corresponding control days, except for the last event (when an increase in function was observed). The largest decrements for $FEV_{1.0}$ and PEFR (48 to 66 mL decline for $FEV_{1.0}$) were observed on the morning after the highest H_2SO_4 event, on July 25, 1986. No analyses were presented, however, that attempted to separate out pollutant effects of H_2SO_4 from those of O_3.

Airway hyper-responsiveness was assessed using a methacholine bronchial provocation test for 96 of the subjects in the Raizenne et al. (1989) study. Children with a positive response to methacholine challenge had larger decrements compared to their nonresponsive counterparts. These preliminary results do not allow definitive statements to be made on the susceptibility of methacholine sensitive subjects. However, there are indications in these data of differential lung function profiles and responses to air pollutants in children with and without airway hyper-responsiveness. Further analyses and research are indicated.

At the same camp, twelve young females (9 to 14 years old) performed pre- and post-exercise spirometry on a day of low air pollution and at the peak of an air pollution episode. Clinical interview, atopy, and methacholine airway hyper-responsiveness tests were performed at the camp on the first 2 days of the study. Seven subjects had positive responses to methacholine challenge ($^+$MC) and five did not ($^-$MC). A standardized ergonometric physical capacity test was also administered, in which minute volume, heart rates, and total work achieved were recorded. Air monitoring was performed on site and, during the episode, air pollution concentrations were: O_3 exceeded 130 ppb; H_2SO_4 exceeded 40 $\mu g/m^3$ during a 1-h period. For the entire group (N = 12), post exercise FVC and $FEV_{1.0}$ were observed to increase on the control day and decrease on the episode day. On the control day, an average 40 mL increase in FVC due to exercise was observed ($p < .05$) for the whole group, with a 71 mL increase in +MC subjects and a 17 mL increase in -MC subjects. Although not statistically significant at $P < 0.10$, the mean FVC for the

entire group was 30 ml less on the day of high pollution versus low pollution, and this difference was more pronounced in -MC (-65 mL) than +MC (-4 mL) subjects. The effect of exercise in the model was statistically significant ($p < .05$), whereas the pollution day effect was not. These results suggest that lung function responses to exercise differ in +MC and -MC subjects under field research conditions, and that the expected normal FVC response to exercise in both groups is altered during periods of elevated ambient pollution. However, no analyses were presented that directly evaluated possible acid aerosol relationships to health effects.

It is of interest to compare results obtained in this summer camp study to findings of certain controlled human exposure studies or to other epidemiology studies. For example, Spengler et al. (1989) calculated that the children in the Raizenne et al. (1989) study received an average 1-h respiratory tract dose of 1050 nmoles of H^+, based on a exposure model which takes into account both the concentration of exposure, and the minute ventilation rate, but not the possible mitigating effects of airway ammonia. Spengler et al. (1989) further noted that the asthmatic subjects in the human clinical studies of Utell et al. (1983) and Koenig et al. (1983) had experienced an airway dose of approximately 1,200 nmoles of H^+, which evoked a response at reported concentrations of 450 $\mu g/m^3$ and 100 $\mu g/m^3$ H_2SO_4, respectively. These calculations suggest that, because of differences in minute ventilation rates, the peak levels occurring at Camp Kiawa during an ambient acid aerosol event may have produced exposures similar to those seen in clinical studies of asthmatic subjects. It remains to be determined as to what extent comparable C x T total respiratory tract dose(s) for H^+ ions may be effective in producing pulmonary function decrements beyond the short exposure times employed in the controlled human exposure studies or in producing other types of effects. For example, Spektor et al. (1989) found that increasing the length of exposure to 100 $\mu g/m^3$ sulfuric acid from 1- to 2-h increased average tracheobronchial clearance half-time from 100 to 162 percent, relative to control.

Studnicka et al. (1995) conducted a study of the effects of air pollution on the lung function of three consecutive panels of children participating in a summer camp in the Austrian Alps during the summer of 1991. On-site environmental assessment consisted of 24-h measurements of PM_{10}, H^+, and $SO_4^=$, as well as continuous measurements of O_3, temperature, and relative humidity. Pollen counts were sampled daily using a Burkhardt spore trap. SO_2 and NO_2 data were obtained from routine monitoring stations located at the same altitude 20 to 30 km from the camp. For 47,

45, and 41 subjects, daily FEV_1, FVC, and peak expiratory flow were recorded. While mean levels of ambient pollutants were generally 15% higher for Panel 1, the Panel 1 H^+ concentrations averaged twice as high as for the other two panels. The maximum H^+ exposure (during Panel 1) was 84 nmol/m^3 (4μg/m^3 H_2SO_4 equivalent). Compared with other camp studies discussed above, peak H^+ exposure was of lesser concentration, but of longer duration.

For FEV_1, a significant decrease of -.099 ml per nmol/m^3 H^+ ($p = 0.01$) occurred during Panel 1. Exclusion of the first 5 days or excluding the maximum H^+ day did not significantly alter this result. The FEV_1/H^+ coefficient was found to be similar (-0.74 ml per nmol/m^3 H^+; $p = 0.28$) for Panel 2, but was in the opposite direction and clearly non-significant during Panel 3 (0.10 ml per nmol/m^3 H^+; $p = 0.83$). The decrease in FEV_1 during Panel 1 was more pronounced when the mean exposure during the previous 4 days (4-d) was used (-2.99 ml; FEV_1 per nmol/m^3 H^+; $p = 0.004$), suggesting greater effects from multiple-day episodes. However, it is important to note that, while O_3 levels were low and not significantly correlated with FEV_1 throughout this study, PM_{10} measurements showed associations of similar strength with FEV_1 during Panel 1 as were found for H^+ ($r_{PM10\ H^+} = 0.94$). Also, in a simultaneous model of FEV_1 on H^+ with PM_{10}, O_3, and pollen in the model, the previous 4-d mean H^+ variable's coefficient was of similar magnitude as for the single pollutant model (though the coefficient SE did rise). This indicates that the H^+ association with FEV_1 remained, even after controlling for other potentially confounding factors. The authors conclude that a significant FEV_1 decrease of 200 ml was observed in children at this camp during a summer haze episode in the Austrian Alps, and the acidic PM may, therefore, be associated with transient decreases in lung function in children. However, PM_{10} showed more of a relationship than did the other pollutants such as H^+.

Studies of Respiratory Symptoms and Pulmonary Function in Schoolchildren

As part of the 6-Cities study conducted by Harvard University, a cohort of approximately 1800 children in grades two through five from six U.S. cities (Watertown, MA; Kingston-Harriman, TN; St. Louis, MO; Portage, WI; Steubenville, OH, and; Topeka, KS) was enrolled in a diary study in which parents completed a bi-weekly report on each child's daily respiratory symptoms (Schwartz et al., 1994). The study extended over 4 school years (1984 to 1988), but data were collected for only one year in each city. Environmental variables measured daily at a

central site in each city included PM_{10}, $PM_{2.5}$, $PM_{2.5}$ sulfur, H^+, H_2SO_4, SO_2, O_3, and nephelometry (a measurement of aerosol scattering of light, which provides an index of sub-micron particle concentration). The H_2SO_4 data were not analyzed in this work. The reported analysis was limited to April through August in each city to reduce seasonal confounding (n = 153). Statistical analyses involved the use of ordinary logistic regression, in which the logarithm of the odds of the response rate is modeled as a linear function of covariates, followed by the application of logistic methods incorporating corrections for autocorrelation using the GEE model proposed by Liang and Zeger (1986) and Zeger and Liang (1986) for such repeated measures studies. Regressions included a temperature and a temperature squared term, as well as city-specific and day of week dummy variables and interaction terms for city-specific temperature terms. Exploratory analyses considered pollution lags of up to 14 days. Pollutants were considered individually in the regressions, and those which were significant individually were considered in multiple pollutant models.

Lower respiratory symptoms (LRS) is defined as the reporting of at least two of: cough, chest pain, phlegm, or wheeze. Analyses of daily LRS found in individual pollutant regressions that PM_{10}, $PM_{2.5}$, $PM_{2.5}$ sulfur (i.e., sulfates), nephelometry, SO_2, and O_3 were all significant predictors. Of all these pollutants, $PM_{2.5}$ sulfur (i.e., sulfates) and PM_{10} yielded the highest levels of significance (t = 3.35 and t = 3.47, respectively), suggesting that it is the sulfur containing fine aerosol component which was driving the PM relationships found with LRS. In the overall data analysis, aerosol acidity was not significantly associated with LRS, but associations were noted for H^+ above 110 nmoles/m^3, with a relative odds ratio of LRS estimated to be greater than 2.0 at 300 nmoles/m^3 H^+ (see Figure 12-4). Similarly, the 6-City diary analysis of upper respiratory symptoms (URS, defined as any two of hoarseness, sore throat, or fever) showed no consistent association with H^+ until concentrations exceeded 110 nmoles/m^3. The exposure-dependent increase in symptoms seen across the entire range of PM_{10} certainly suggests that the effect is principally related to particle mass, and not specifically to the acidic components. Acid may increase the particulate effect if it is in high enough concentrations, however. This may relate to neutralization of lower concentrations of acidic aerosols by ammonia in the breathing zone. Further investigation of any role of aerosol acidity in modulating the effects of PM_{10} is needed to clarify this.

A separate analysis of upper respiratory symptoms was also conducted using similar data and methods for three of the cities only: Watertown, MA; Kingston-Harriman, TN; St. Louis, MO (Schwartz et al., 1991b). In these cities, the pollutant with the largest regression coefficient was H_2SO_4 , with the strongest association falling on the prior two days. Unfortunately, comparative details about other pollutants are not provided in this paper. While sketchy, these results are consistent with the hypothesis that ambient acid aerosols in general, and H_2SO_4 in particular, may be associated with health effects in children.

In a study of ambient air pollution and lung function in children reported by Neas et al. (1995), a sample of 83 children living in Uniontown, PA performed twice daily peak expiratory flow rate (PEFR) measurements on 3,582 child-days during the summer of 1990. Upon arising and before retiring, each child recorded the time, three PEFR measurements, and the presence of cold, cough, or wheeze symptoms. Environmental factors were monitored, including ambient temperature, O_3, SO_2, fine particle mass, PM_{10}, and particle strong acidity, which was measured separately during the day (8 am to 8 pm) and night. Each child's maximum PEFR for each session was expressed as the deviation from their mean PEFR over the study and adjusted to a standard of 300 liters/minute. The session-specific average deviation was then calculated across all the children. A second order autoregressive model for PEFR was developed which included a separate intercept for evening measurements, trend, temperature, and 12-h average air pollutant concentration weighted by the number of hours each child spent outdoors during the previous 12-h period. A 12-h exposure to a 125 nmole/m_3 increment in H^+ was associated with a -2.5 liters/minute deviation in the group mean PEFR (95% CI = -4.2 to -0.8) and with increased cough incidence (odds ratio, OR = 1.6; 95% CI = 1.1 to 2.4). It should be noted, however, that H^+ was highly correlated with sulfates (r = 0.92) and fine particles (r = 0.86). A 30 ppb increment in ozone for 12-h was associated with a similar deviation in PEFR levels (-2.8; 95% CI = -6.7 to 1.1). However, when both O_3 and H^+ were entered into the model simultaneously, the H^+ effect size was only slightly reduced and remained significant. Although monitored, PM_{10} results were not presented for comparison. The association between PEFR and particle strong acidity was observed among the 60 children who were reported as symptomatic on the prior symptom questionnaire (-2.5; 95% CI = -4.5 to -0.5). The authors concluded that summertime occurrences

of elevated acid aerosol and particulate sulfate pollution are associated with acute declines in peak expiratory flow rates and increased incidence of cough episodes in children.

Overall, most of these camp and school children studies provide evidence indicating an acute acidic PM effect on both children's respiratory function and symptoms. However, given the usually high correlation between acidic PM and PM in these studies, it is difficult to identify these effects solely with the acid portion of PM.

12.5.3.5 Acute Acid Aerosol Exposure Studies of Adults

Acute Acid Aerosol Exposures and Asthma Symptoms in Adults

The hypothesis that human exposures to ambient H^+ concentrations are associated with exacerbations of pre-existing respiratory disease was tested by a recent study of asthmatic responses to airborne acid aerosols (Ostro et al., 1989, 1991). Data on daily concentrations of aerosol H^+, SO_4, NO_3, and FP, as well as gaseous SO_2 and HNO_3, were tested for correlation with daily symptom, medication usage, and other variables for a panel of 207 adults with moderate to severe asthma in Denver, CO between November 1987 and March 1988. However, CO and NO_2, potentially confounding pollutants, were not considered in the analyses. The H^+ concentrations ranged from 2 to 41 neq/m^3 (0.01 to 2.0 µg/m^3 of H_2SO_4 equivalent), and were significantly related to both the proportion of the survey respondents reporting a moderate or worse overall asthma condition, and the proportion reporting a moderate or worse cough. However, it is important to note that these concentrations are near to or below the level of detection of H^+, and that, of the 74 H^+ values used in the analysis, 47 were predicted from the observed $SO_4^=$ value on that day (H^+ - $SO_4^=$ correlation = 0.66), which is more accurately measured at such low levels. $PM_{2.5}$ was also highly correlated with sulfates during this study (r = 0.86). Both logit models and ordinary least squares with a log pollution term, autoregressive terms, and terms for trend, weekend, use of gas stove, and maximum daily temperature were modeled.

Of all the pollutants considered in these analyses, H^+ displayed the strongest associations with asthma and cough. In the first analysis, the magnitudes of effects were compared by computing elasticities, or the percent change in the health effect due to a given percent change in the pollutant. The results for asthma indicated elasticities with respect to SO_4, FP, and H^+ of 0.060, 0.055 and 0.096, respectively (Ostro et al., 1989). This indicates that a doubling of the

concentration of H^+ (from 8 to 16 nmoles/m^3) would increase the proportion reporting a moderate to severe asthma condition by 10 percent. In their follow-up report on this study, Ostro et al. (1991) examined evidence for lagged effects, and concluded that contemporaneous measures of H^+ concentration provided the best associations with asthma status, and that meteorological variables were not associated with the health effects reported. They also examined the effects of exposure to H^+, adjusting for time spent outdoors, level of activity, and penetration of acid aerosol indoors. Based on the adjusted exposures, the effect of H^+ on cough increased 43%, suggesting that dose-response estimates that do not incorporate behavioral factors affecting actual H^+ exposures may substantially underestimate the impact of the pollution. The associations of exposure adjusted H^+ with moderate to severe cough and with asthma status are shown in Figures 12-13 and 12-14, respectively. Although the H^+ concentrations on some days had to be estimated from sulfates, and potentially confounding pollutants were not considered simultaneously with H^+ in the model, these results allow the consideration that human exposures to present day ambient H^+ concentrations may be associated with exacerbations of pre-existing respiratory disease.

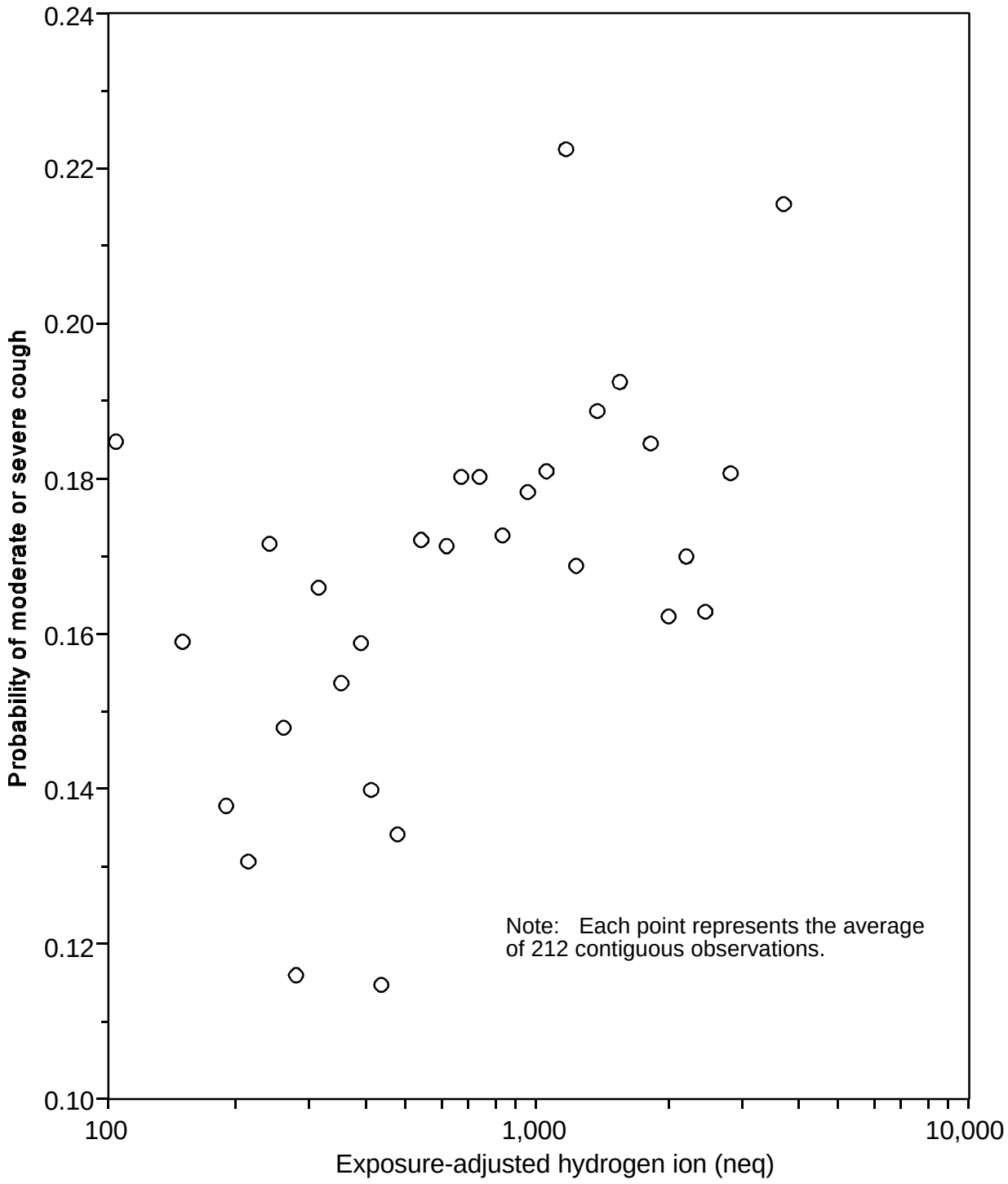

Figure 12-13. Association of moderate or severe cough with exposure-adjusted hydrogen ion.

Source: Ostro et al. (1991).

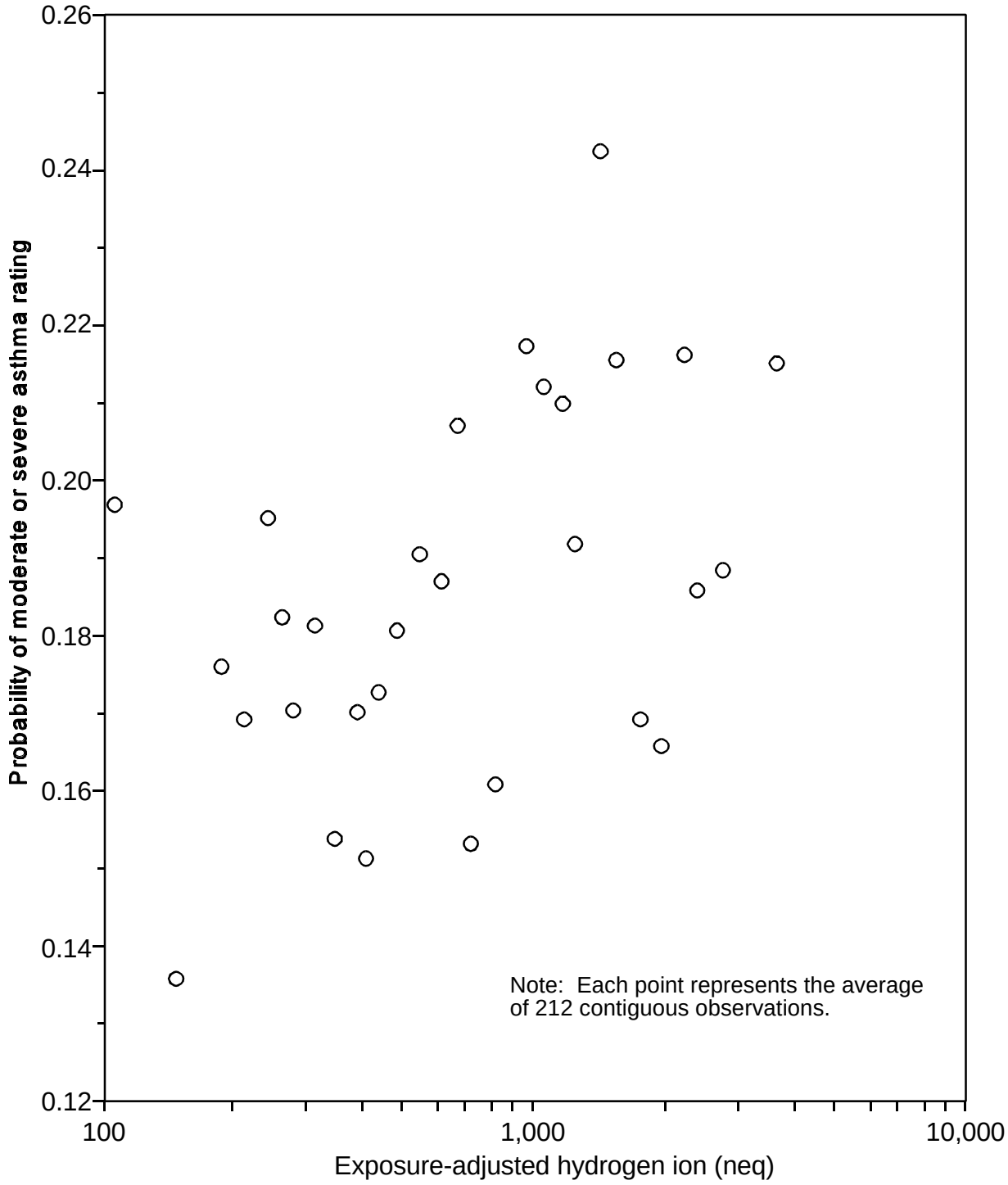

Figure 12-14. Association of moderate or severe asthma rating with exposure-adjusted hydrogen ion.

Source: Ostro et al. (1991).

12.5.3.6 Acute Acidic Aerosol Associations with Respiratory Hospital Admissions

The reported sulfate-respiratory hospital admissions associations discussed above were interpreted as potentially being due to the presence of strongly acidic aerosols on high sulfate days. Two follow-up studies of respiratory hospital admissions were conducted in New York State and in Toronto, Ontario to directly test this hypothesis.

Thurston et al. (1992) analyzed unscheduled (emergency) admissions to acute care hospitals in three New York State metropolitan areas during the summers of 1988 and 1989. Environmental variables considered included daily 1-h maximum ozone, 24-h sulfate, and particulate strong acid aerosol (H^+) concentrations, as well as daily maximum temperature recorded at central sites in each community. For this study, acid aerosols were sampled in residential suburbs of Buffalo, Albany, and New York City (NYC), NY. In NYC, the site was located well outside the urban core (in White Plains, 10 mi. north of the city), so the acid levels are likely to be overestimates of the levels experienced directly in the city. Comparisons between sulfates in the White Plains site and at a site in Manhattan during part of the study period showed a high correlation ($r = 0.9$), supporting the assumption that the White Plains H^+ data are indicative of particulate strong acid exposures in NYC. Long wave periodicities in the data were reduced by selecting a June through August study period. However, because of remaining within-season long wave cycles in the data series, they were prefiltered using sine and cosine waves with annual periodicities. Day of week effects were also controlled via regression. These adjustments resulted in non-significant autocorrelations in the data series and also improved the pollution correlations with admissions.

The strongest pollutant-respiratory admissions associations found by Thurston et al. (1992) were during the high pollution 1988 summer and in the most urbanized communities considered (i.e., Buffalo and New York City). Correlations between the pollution data and hospital admissions for non-respiratory control diseases were non-significant both before and after prefiltering. After controlling for temperature effects via simultaneous regression, the summer haze pollutants (i.e., $SO_4^=$, H^+, and O_3) remained significantly related to total respiratory and asthma admissions. However, multiple pollutant regressions were not attempted, preventing a clear discrimination of the respective effects of these pollutants. Other community pollutants (e.g., NO_2, SO_2, and CO) were not considered, but are generally low and unlikely to be highly

correlated with the studied pollutants during July and August in these cities. After filtering, $SO_4^=$ and H^+ were highly correlated in these cities (e.g., r = 0.86 in Buffalo, and 0.79 in NYC during the summer of 1988), supporting the contention that SO_4 is a useful index of H^+ in such time-series analyses. In regressions for the summer of 1988 for Buffalo and New York City, both H^+ and $SO_4^=$ had similar mean effects (3 to 4% of respiratory admissions in NYC, at mean H^+ = 2.4 μg/m^3 as H_2SO_4, and mean $SO_4^=$ = 9.3 μg/m^3; and 6 to 8% in Buffalo, at mean H^+ = 2.2 μg/m^3 as H_2SO_4, and mean $SO_4^=$ = 9.0 μg/m^3). Ozone mean effects estimates were always larger than for H^+ or $SO_4^=$, but the impact of the highest day was greatest for H^+ in all cases. This is the case in part because H^+ episodes are more extreme, relative to the mean, than are O_3 episodes (e.g., in Buffalo in 1988, the summer max./mean H^+ = 8.5, while the max./mean O_3 = 2.2). Thus, the maximum H^+ day in Buffalo (18.7 μg/m^3 as H_2SO_4, or 381 nmoles H^+/m^3, on August 4, 1988), was estimated to be associated with a 47% increase above the mean number of total respiratory admissions in this metropolitan area (mean = 25/day). Thus, the H^+ effects estimates reported in this work are dominated by the two or three peak H^+ days per year experienced in these cities (e.g., H^+ > 10 μg/m^3, or ~200 nmoles/m^3, as a 24-h average).

Thurston et al. (1994b) focused their analysis of respiratory hospital admissions in the Toronto metropolitan area during the summers (July to August) of 1986 to 1988, when they directly monitored for strong particulate acidity (H^+) pollution on a daily basis in that city. This study was designed specifically to test the hypothesis that the $SO_4^=$ associations found in southern Ontario by Bates and Sizto were due to H^+ exposures. Acid measurements were made at three sites in the Toronto metropolitan area, and were found to be highly correlated across sites (Thurston et al., 1994a). The H^+ data from the center city site (Breadalbane St.) were used for the health effects analyses, as there were a full 3 summers of data there (the other two sites were not operated in 1988), and because other pollutants were measured there daily, as well. The 9AM to 5PM average H^+ was employed in these analyses. Long wave cycles, and their associated autocorrelations, were removed by first applying an annual periodicity sine-cosine fit to the data (as well as day of week dummy variables) and analyzing the resulting residuals. Strong and significant positive associations with both asthma and respiratory admissions were found for both O_3 and H^+, and somewhat weaker significant associations with $SO_4^=$. No such associations were found for SO_2 or NO_2, nor for any pollutant with non-respiratory control admissions. Other PM

metrics examined included the mass of fine particles less than 2.5 μm in d_a (FP), the mass of particles greater than 2.5 μm and less than 10 μm in d_a (CP), PM_{10} (= FP+CP), TSP, and non-thoracic TSP (= TSP-PM_{10}). Temperature was only weakly correlated with respiratory admissions, and became non-significant when entered in regressions with air pollution indices.

Simultaneous regressions and sensitivity analyses indicated that O_3 and H^+ were the summertime haze constituents of greatest importance to respiratory and asthma admissions in Toronto during these three summers. Indeed, as shown in Table 12-23, of the PM metrics considered, only H^+ remained significant in the respiratory admissions regression with both O_3 and temperature also included. The correlation of the H^+ and O_3 coefficients in this simultaneous model was non-significant (r=-0.11), indicating that these two pollutants have independent associations with respiratory admissions. As shown in Table 12-24, the 1988 results for Toronto are consistent with (i.e., not statistically different from) those found previously for nearby Buffalo, NY (approximately 100 km to the south, across Lake Ontario). As in these authors' Buffalo analysis, the maximum H^+ day in Toronto (August 4, 1988: H^+ = 391 nmoles/m^3) was estimated to be associated with the greatest relative risk of total respiratory and asthma admissions (1.50 and 1.53, respectively), again indicating an especially large adverse respiratory effect by summertime haze air pollutants during the few H^+ episode days each summer. However, a sensitivity analysis eliminating the six days having H^+ 100 nmoles/m^3 yielded a similar, and statistically significant, H^+ coefficient in the total respiratory admissions regression, suggesting that the association is not limited to the highest pollution days alone. The authors reviewed A.B. Hill's criteria for causality (Hill, 1965), and concluded that the associations they report between summertime haze air pollutants (i.e., O_3 and H^+) and acute exacerbations of respiratory disease (i.e., respiratory hospital admissions) are causal. It is of particular interest to note that, assuming the H^+ to be in the form of NH_4HSO_4, the "effect" per μg/m^3 of mass implied by these Toronto coefficients indicate that H^+ is six times as potent (per μg/m^3) as non-acidic PM_{10}.

TABLE 12-23. SIMULTANEOUS REGRESSIONS OF 1986 TO 1988 TORONTO DAILY SUMMERTIME TOTAL RESPIRATORY ADMISSIONS ON TEMPERATURE AND VARIOUS POLLUTION METRICS

Temp, pollutant model specification	Pollutant Regression Coefficients (adm/poll unit[a])	*P* value (one-sided)
	Two pollutant models	
T(LG0), O_3(LG0)[b]	0.0503 ± 0.0205	0.008
H^+(LG1)	0.0153 ± 0.0089	0.044
T(LG0), O_3(LG0)	0.0508 ± 0.0207	0.008
$SO_4^=$(LG1)	0.0062 ± 0.0046	0.089
T(LG0), O_3(LG0)	0.0404 ± 0.0233	0.043
FP(LG0)	0.0434 ± 0.0429	0.157
T(LG0), O_3(LG0)	0.0388 ± 0.0241	0.055
PM_{10}(LG0)	0.0339 ± 0.0344	0.164
T(LG0), O_3(LG0)	0.0360 ± 0.0228	0.059
TSP(LG0)	0.0127 ± 0.0175	0.235

[a]Pollution units: nmole/m^3 for H^+ and $SO_4^=$; ppb for O_3; and $\mu g/m^3$ for FP, CP, PM_{10}, TSP, TSP-PM_{10}.
[b]LGO: zero day lag; LG1: one day lag.

Source: Thurston et al. (1994b)

These two new studies of daily respiratory hospital admissions in New York State cities and in Toronto, Ontario support the hypothesis that the summertime sulfate concentrations previously found to be correlated with respiratory admissions are indeed accompanied by acidic aerosols in Eastern North America. Furthermore, in these recent analyses, the H^+ associations with respiratory hospital admissions were found to be stronger than for sulfates, or any other PM component monitored. The facts that: (1) these were studies designed specifically to test the hypothesis that H^+ is associated with increased respiratory hospital admissions; (2) consistent results were found, both qualitatively and quantitatively across these studies, and; (3) in one of them, many other pollutants and PM metrics were directly intercompared with H^+ in the analyses, collectively indicate that these studies provide evidence that acidic aerosols may represent a component of PM which is particularly associated with increases in the incidence of exacerbations in pre-existing respiratory disease.

TABLE 12-24. COMPARISON OF REGRESSIONS OF DAILY SUMMERTIME RESPIRATORY ADMISSIONS ON POLLUTION AND TEMPERATURE IN TORONTO, ONTARIO, AND BUFFALO, NEW YORK 1988 SUMMER

City and year	Respiratory admissions category	Temp, pollutant model specification	Pollutant Regression Coefficient (adm/$\mu g/m^3/10^6$, persons ±SE)	Pollutant mean effect (% ±SE)	Max/mean pollutant rel risk (±SE)
Toronto, 1988 summer	Total respiratory (mean = 14.1/day)	T(LG2), $SO_4^=$(LG1)	0.07 ± 0.03[a]	13.3 ± 5.3	1.41 ± 0.16
		T(LG2), H^+(LG1)	0.18 ± 0.009[b]	7.7 ± 3.9	1.50 ± 0.25
		T(LG2), O_3(LG1)	0.011 ± 0.005[b]	26.4 ± 11.8	1.34 ± 0.15
Toronto, 1988 summer	Total asthma (mean = 9.5/day)	T(LG2), $SO_4^=$(LG1)	0.04 ± 0.02[b]	13.0 ± 6.8	1.40 ± 0.21
		T(LG2), H^+(LG0)	0.13 ± 0.07[b]	8.1 ± 4.5	1.53 ± 0.29
		T(LG2), O_3(LG1)	0.007 ± 0.004[b]	25.3 ± 14.9	1.32 ± 0.19
Buffalo, 1988 summer	Total respiratory (mean = 25.0/day)	T(LG2), $SO_4^=$(LG0)	0.11 ± 0.04[a]	8.0 ± 2.7	1.25 ± 0.09
		T(LG2), H^+(LG0)	0.35 ± 0.12[a]	6.4 ± 2.2	1.47 ± 0.16
		T(LG2), O_3(LG2)	0.015 ± 0.008[b]	18.4 ± 9.9	1.22 ± 0.12
Buffalo, 1988 summer	Total asthma (mean = 7.1/day)	T(LG2), $SO_4^=$(LG1)	0.03 ± 0.02[b]	7.0 ± 3.9	1.25 ± 0.14
		T(LG2), H^+(LG1)	0.09 ± 0.05[b]	5.6 ± 3.3	1.43 ± 0.26
		T(LG2), O_3O(LG3)	0.006 ± 0.002[a]	23.9 ± 10.1	1.29 ± 0.12

[a]P<0.01 (one-way test).
[b]P<0.05 (one-way test).

Sources: Thurston et al. (1994b) and Thurston et al. (1992).

12.5.3.7 Acute Acid Aerosol Exposure Associations with Mortality

As discussed in the methodological discussions at the outset of this chapter, relatively long records of daily mortality and pollution are required to have sufficient power to discern mortality-pollution associations. Due to the dearth of sufficiently long records of H^+ measurements (other than the historical London measurements discussed previously), only a few studies have attempted to evaluate the acute mortality effects of acidic aerosols.

Dockery et al. (1992) investigated the relationship between multiple air pollutants and total daily mortality during the one year period between September 1985 and August 1986 in two communities: St. Louis, MO; and Kingston/Harriman, TN and surrounding counties. In the latter locale, the major population center considered is Knoxville, TN, some 50 Km from the air pollution monitoring site employed. In each study area, total daily mortality was related to PM_{10}, $PM_{2.5}$, SO_2, NO_2, O_3, $SO_4^=$, H^+, temperature, dew point, and season using autoregressive Poisson models. In St. Louis, after controlling for weather and season, statistically significant associations were found with both prior day's PM_{10} and $PM_{2.5}$, but not with any lags of the other pollutants considered. In the Kingston/Harriman vicinity, PM_{10} and $PM_{2.5}$ approached significance in the mortality regression, while the other pollutants did not. In both cities, very similar PM_{10} coefficients are reported, implying a 16 to 17 percent increase in total mortality per 100 $\mu g/m^3$ of PM_{10}. While autocorrelation was accounted for, seasonality was addressed by season indicator (dummy) variables, which may not remove within-season long wave influences. However, the chief areas of concern regarding this study relate to the exposure data. In both places, only one daily monitoring station was employed to represent community exposure levels, and no information regarding the representativeness of these sites are provided (e.g., correlations with other sites' data). More importantly in the case of H^+ analyses, the number of days for which pollution data are available for time-series analyses is limited in this data set (e.g., only 220 days had H^+ values at the St. Louis site). As discussed in the methodological section, it is expected that roughly at least twice this number of study days are needed to be able to reliably detect PM associations with mortality. Thus, in the words of the authors: "Because of the short monitoring period for daily particulate air pollution, the power of this study to detect associations was limited." A latter data set for six cities (Schwartz et al., 1996) that was also not significant for H^+ was discussed in detail earlier in Section 12-3.

Thus, this attempt to correlate human mortality with present day ambient acid aerosol concentrations was unable to find a significant association, but it is not clear to what extent this result was due to the severe lack of power in the analysis (because of the many fewer H^+ observations than available for other pollutants). Clearly, there is a critical need for present day replications of the London mortality-acid aerosol studies to be conducted, in order to determine whether these London associations (dominated by wintertime H^+, occurring in reduction-type atmospheres) are pertinent to the U.S., where acid aerosol peaks occur primarily in the summertime, in oxidation-type atmospheres.

12.5.4 Studies Relating Health Effects to Long-Term Exposure

A limited but growing amount of epidemiologic study data currently exist by which to evaluate possible relationships between chronic exposures to ambient acid aerosols and human health effects. These include one study from Japan relating effects to estimated or measured acidity, and many other North American studies which relate effects to sulfate levels or other surrogate measures thought to roughly parallel acid aerosol concentrations. Moreover, newer epidemiologic studies, which consider measured acid aerosols, now provide more direct insight into the potential chronic effects of particulate strongly acidic aerosols.

12.5.4.1 Acid Mists Exposure in Japan

Kitagawa (1984) examined the cause of the Yokkaichi asthma events (1960 to 1969) by examining the potential for exposure to concentrated sulfuric acid mists and the location and type of health effects noted. He concluded that the observed respiratory diseases were due not to sulfur dioxide, but to concentrated sulfuric acid mists emitted from stacks of calciners of a titanium oxide manufacturing plant located windward of the residential area. This was based on the fact that the SO_3/SO_2 ratio of 0.48 was much higher than the normal range of 0.02 to 0.05. The higher ratio indicates a higher acid aerosol level. The acid particles were fairly large (0.7 to 3.3 μm) compared with acid aerosols usually seen in the United States of America (see Chapter 3), but were still were in the respirable range. Between 1960 and 1969, more than six hundred patients with respiratory disease were found to have chronic bronchitis, allergic asthmatic bronchitis, pulmonary emphysema and sore throat. In 1969, measures of acid aerosol exposures

were obtained from litmus paper measurements collected near the industrial plant which showed that acid mist particles were distributed leeward of the industrial plant. The author notes that the physiological effects of concentrated sulfuric acid mists (per estimated mass concentration) may be quite different from that of dilute sulfuric acid mists formed by atmospheric oxidation of sulfur dioxide, and that the distinction between the two types of acid mists is very important. It should be noted that morbidity fell markedly after the installation of electrostatic precipitators which reduced H_2SO_4 and other particulate matter emissions.

12.5.4.2 Studies Relating Chronic Health Effects to Sulfate Exposures

Franklin et al. (1985) and Stern et al. (1989) reported on a cross-sectional study investigating the respiratory health of children in two Canadian communities that was conducted in 1983 to 1984, in Tillsonburg, Ontario and Portage la Prairie, Manitoba. There were no significant local sources of industrial emissions in either community. In the first town, 735 children aged 7 to 12 were studied and 895 in the second one. Respiratory health was assessed by the measurement of the forced vital capacity (FVC) and forced expiratory volume in 1 s ($FEV_{1.0}$) of each child, and by evaluation of respiratory symptoms and illnesses using a questionnaire self-administered by the parents. While NO_2 and inhalable particles (PM_{10}) differed little between these communities, SO_2, SO_4, and NO_3 were higher in Tillsonburg. Historical data in the vicinity of Tillsonburg indicate that average levels of sulfates, total nitrates and ozone (O_3) did not vary markedly in the 9-year period proceeding the study. The results show that Tillsonburg children had statistically significantly ($p < 0.001$) lower levels of FVC and $FEV_{1.0}$ than the children in Portage la Prairie (2% and 1.7% lower, respectively). These differences could not be explained by parental smoking or education, cooking or heating fuels, pollution levels on the day of testing or differences in age, sex, height or weight. The differences persisted when children with either cough with phlegm, asthma, wheeze, inhalant allergies or hospitalization before age 2 for a chest illness were excluded from analysis. With the exception of inhalant allergies, which occurred more frequently in Tillsonburg children, the prevalence of chronic respiratory symptoms and illnesses was similar in the two towns. Thus, sulfates were among the pollutants which were higher in the community experiencing reduced lung function and increased inhalant allergies, while PM_{10} mass concentrations were not different between cities.

Ware et al. (1986) have reported results of analyses from the ongoing Harvard study of outdoor air pollution and respiratory health status of children in six eastern and midwestern U.S. cities. Between 1974 and 1977, approximately 10,100 white preadolescent children were enrolled in the study during three successive annual visits to the cities. On the first visit, each child underwent a spirometric examination, and a parent completed a standardized questionnaire regarding the child's health status and other important background information. Most of the children (8,380) were seen for a second evaluation one year later. Data on TSP, SO_4, and SO_2 concentrations at study-affiliated outdoor stations were combined with data from other public and private monitoring sites to create a record of pollutant levels in each of nine air pollution regions during a one-year period preceding each evaluation, and for TSP during each child's lifetime up to the time of evaluation. Annual mean TSP levels ranged from 32 to 163 $\mu g/m^3$. Sulfur dioxide levels ranged from 2.9 to 184 $\mu g/m^3$, and sulfate levels ranged from 4.5 to 19.3 $\mu g/m^3$.

Analyzing these data across all six cities, Ware et al. (1986) found that frequency of chronic cough was significantly associated ($p < 0.01$) with the average of 24-h mean concentrations of TSP, SO_2, and SO_4 air pollutants during the year preceding the health examinations. Furthermore, rates of bronchitis and a composite measure of lower respiratory illness were significantly ($p < 0.05$) associated with annual average particle concentrations. However, within the individual cities, temporal and spatial variation in air pollutant levels and symptom or illness rates were not found to be significantly associated. The history of early childhood respiratory illness for lifetime residents was significantly associated with average TSP levels during the first two postnatal years within cities, but not between cities. Also, pulmonary function parameters (FVC and $FEV_{1.0}$) were not associated with pollutant concentrations during the year immediately preceding the spirometry test or, for lifetime residents, with lifetime average concentrations. Ferris et al. (1986), however, reported a small effect on lower airway function (MMEF) related to fine particle concentrations. Spengler et al. (1986) report the occurrence of acid aerosol peak concentrations of 30 to 40 $\mu g/m^3$ (1 h average) in two of the cities during recent monitoring. Overall, these results appear to suggest that risk may be increased for bronchitis and some other respiratory disorders in preadolescent children at moderately elevated levels of TSP, SO_4, and SO_2 concentrations, which do not appear to be consistently associated with pulmonary function

decrements. However, the lack of consistent significant associations between morbidity endpoints and air pollution variables within individual cities argues for caution in interpreting these results.

Dockery et al. (1989) presented further results from the cross-sectional assessment of the association of air pollution with chronic respiratory health of children participating in the Six Cities Study of Air Pollution and Health. Air pollution measurements collected at quality-controlled monitoring stations included total suspended particulate matter (TSP), particulate matter less than 15 μm (PM_{15}) and 2.5 μm ($PM_{2.5}$) aerodynamic diameter, fine fraction aerosol sulfate ($SO_4^=$), SO_2, O_3, and NO_2. This analysis was restricted to the 5,422 10 to 12 years old white children examined in the 1980 to 1981 school year. Five respiratory illness and symptom responses obtained by questionnaire were considered: bronchitis, cough, chest illness, wheeze, and asthma. Each symptom was analyzed using a logistic regression model including sex, age, indicators of parental education, maternal smoking, gas stove, and city. Reported rates of bronchitis, chronic cough, and chest illness during the 1980 to 1981 school year were positively associated with all measures of particulate pollution (TSP, PM_{15}, $PM_{2.5}$, and SO_4) and positively, but less strongly, associated with concentrations of two of the gases (SO_2 and NO_2). For children experiencing wheeze, the estimated relative odds (and 95% CI) for $SO_4^=$ between the most and least polluted cities were: 3.1 (0.6 to 16.8) for bronchitis; 2.4 (0.1 to 60.6) for chronic cough, and; 2.9 (0.5 to 15.6) for chest illness. Frequency of earache also tended to be associated with particulate concentrations, but no significant associations were found with asthma, persistent wheeze, hay fever, or non-respiratory illness. No associations were found between pollutant concentrations and any of the pulmonary function measures considered (FVC, $FEV_{1.0}$, FEV0.75, and MMEF). Children with a history of wheeze or asthma had a much higher prevalence of respiratory symptoms, and there was some evidence that the association between air pollutant concentrations and symptom rates was stronger among children with these markers for hyperreactive airways. Results suggest that children with hyperreactive airways may be particularly susceptible to other respiratory symptoms when exposed to these pollutants. The lack of statistical association between pollutant concentrations and measures of both pulmonary flow and volume suggests, however, that these increased rates of illness are not associated with permanent loss of pulmonary function, at least during the preadolescent years. Overall, these data provide further evidence that rates of respiratory illnesses and symptoms are elevated among

children living in cities with high particulate pollution, including sulfates. Sulfates are known to be correlated over time and across cities with H^+, based on direct $SO_4^=$ and H^+ monitoring subsequently conducted in each of these cities as part of this study.

Dodge et al. (1985) reported on a longitudinal study of children exposed to markedly different concentrations of SO_2 and moderately different levels of particulate sulfate in Southwestern U.S. towns. In the highest pollution area, the children were exposed to 3 h peak SO_2 levels exceeding 2,500 $\mu g/m^3$ and annual mean particulate sulfate levels of 10.1 $\mu g/m^3$. The prevalence of cough (measured by questionnaire) correlated significantly with pollution levels (chi-square for trend = 5.6, p = 0.02). No significant differences existed among the groups of subjects over 3 years, and pulmonary function and lung growth over the study were roughly equal over all groups. The results tend to suggest that intermittent high level exposure to SO_2, in the presence of moderate particulate sulfate levels, produced evidence of bronchial irritation (increased cough), but no chronic effect on lung function or lung function growth. These results are consistent with a bronchitis - H^+ relationship, to the extent that SO_2 or sulfates are indicative of acidic aerosols in these locales.

Chapman et al. (1985) report the results of a survey done in early 1976 that measured the prevalence of persistent cough and phlegm among 5,623 young adults in four Utah communities. The communities were stratified to represent a gradient of sulfur oxides exposure. Community specific annual mean SO_2 levels had been 11, 18, 36, and 115 $\mu g/m^3$ during the five years prior to the survey. The corresponding annual mean sulfate levels were 5, 7, 8, and 14 $\mu g/m^3$. No gradients for TSP or suspended nitrates were observed. The analyses were made using multiple logistic regression, in order to adjust for confounding factors such as smoking, age and education. Persistent cough and phlegm rates in fathers were about 8 percent in the high SO_2/SO_4 exposure community, versus about 3 percent in the other communities. For mothers, the rates in the high SO_2/SO_4 exposure community were about 4 percent, as opposed to about 2 percent in the other communities. Both differences were statistically significant, suggesting that communities with higher SO_2 and SO_4 pollution experience chronically higher respiratory symptom rates in adults.

Stern et al. (1994) reported on a Canadian survey assessing the effects to transported acidic pollution on the respiratory health of children, regional differences in respiratory symptoms and lung function parameters. A cohort of about 4,000 Canadian school children, aged 7 to 11 years,

residing in five rural communities in southwestern Ontario (high exposure area) and in five rural communities in central Saskatchewan (low exposure area) were examined. Respiratory health status was assessed through the use of parent-completed questionnaires and standard pulmonary function tests performed by the children in the schools. The levels of particulate sulfates and nitrates varied little among communities within each region, but sulfate means did differ between regions, with annual average sulfate readings for 1980 of 1.9 $\mu g/m^3$ and 6.6 $\mu g/m^3$ in Saskatchewan and Ontario, respectively. There were no significant differences in PM_{10} between these regions, however. After adjusting for the effects of age, sex, parental smoking, parental education and gas cooking, no differences in the prevalence of chronic cough, chronic phlegm, persistent wheeze, current asthma, bronchitis in the past year, or any chest illness that kept a child home for 3 or more days in the previous year most days and nights were observed. This differs with the results of the Harvard Six City Study (Dockery et al., 1989), which Stern et al. (1994) conclude may be due to a threshold of effects for chronic air pollution and respiratory symptoms effects. There were no regional differences in PEFR, FEF_{25-75}, FEF_{75-85}, $Vmax_{5O}$, and $Vmax_{25}$. However, statistically significant decrements of 1.7% in FVC and 1.3% in $FEV_{1.0}$ were observed in Ontario children, as compared with those in Saskatchewan, after adjusting for age, sex, weight, standing height, parental smoking, and gas cooking. These results are noted to be similar to those reported by Schwartz (1989), but not with the Six-Cites results (Dockery et al., 1989). It is hypothesized that this new study had greater power to detect such effects because the areas being contrasted are more similar, other than with respect to air pollution. The authors conclude that statistically significant decrement in the pulmonary volume parameters, FVC and $FEV_{1.0}$, of preadolescent children residing in rural southwestern Ontario are associated with moderately elevated ambient concentrations of sulfates and ozone.

Schenker et al. (1983b) studied 5,557 adult women in a rural area of western Pennsylvania using respiratory disease questionnaires. Air pollution data (including SO_2, but not particulate matter measurements) were derived from 17 air monitoring sites and stratified in an effort to define low, medium and high pollution areas. The four-year means (1975 to 1978) of SO_2 in each stratum were 62, 66, and 99 $\mu g/m^3$, respectively. Respiratory symptom rates were modeled using multiple logistic regression, which controlled for several potentially confounding factors, including smoking. A model was used to estimate air pollutant concentrations at population-weighted

centroids of 36 study districts. The relative risk (odds ratio) of "wheeze most days or nights" in nonsmokers residing in the high and medium pollution areas was 1.58 and 1.26 (p 0.02) respectively, as compared with the low pollution area. For residents living in the same location for at least five years, these relative risks were 1.95 and 1.40 ($p < 0.01$). Also, the increased risk of grade 3 dyspnea in nonsmokers was associated with SO_2 levels (p 0.11). However, no significant association was observed between cough or phlegm and air pollution variables. The results of this study may indicate that wheezing can be associated with SO_2 levels, but these results must be viewed with caution, since the gradient between areas was small and there were no particle or other pollutant measures. Lippmann (1985) suggested that it was plausible that the effects in this study are associated with submicrometer acid aerosol, which deposits primarily in small airways, rather than with SO_2 levels.

Jedrychowski and Krzyzanowski (1989) related SO_2 and PM levels to increased rates of chronic phlegm, cough and wheezing in females living in and near Cracow, Poland. The authors conjecture that the effects may have been due to hydrogen ions, but no direct measurements were available.

Several authors (Lave and Seskin, 1972, 1977; Chappie and Lave, 1982; Mendelsohn and Orcutt, 1979; Lipfert, 1984; Ozkaynak and Spengler, 1985; Ozkaynak and Thurston, 1987) have related annual mortality rates in U.S. Metropolitan Statistical Areas (MSA's) to sulfate and other pollution measurements using aggregate population cross-sectional analyses. There are significant problems and inconsistencies in results obtained across many of these analyses, as reviewed extensively by the U.S. Environmental Protection Agency (1986a, 1982). For example, Lave and Seskin (1977) reported that mortality rates were correlated with sulfates. Lipfert (1984), reanalyzing the same data using new variables, found that it was not possible to conclude whether sulfates or particulate matter had a statistically significant effect on total mortality in that it was difficult to separate the effects of sulfates from TSP on total mortality, even when sulfate is subtracted from TSP. These studies are reviewed in more detail in Section 12.4.1, but are included again in this section because of their relevance to acid aerosol epidemiology.

Ozkaynak and Spengler (1985), Ozkaynak et al. (1986), and Ozkaynak and Thurston (1987) employed a variety of model specifications and controls for possible confounding, and used more sophisticated statistical approaches in an effort to improve upon some of the previous analyses of

mortality and morbidity associations with air pollution in U.S. cities. The principal findings concern cross-sectional analysis of the 1980 U.S. vital statistics and available air pollution data bases for sulfates, and fine, inhalable and total suspended particles. In these analyses, using multiple regression methods, the association between various particle measures and 1980 total mortality were estimated for 98 and 38 SMSA subsets by incorporating information on particle size relationships and on a set of socioeconomic variables to control for potential confounding. Model misspecification and spatial autocorrelation of the residuals issues were also investigated. Results from the various regression analyses indicated the importance of considering particle size, composition, and source information in modeling of PM-related health effects. In particular, particle exposure measures related to the respirable and/or toxic fraction of the aerosols, such as FP (fine particles) and sulfates were the most consistently and significantly associated with the reported (annual) cross-sectional mortality rates. On the other hand, particle mass measures that included coarse particles (e.g., TSP and IP) were often found to be nonsignificant predictors of total mortality. Part of the relative insensitivity of coarse particles could have resulted from greater spatial variability across an SMSA and the use of a single monitoring station (see Chapter 7). In addition, an analysis of source-related fine particle trace element components for the 38 SMSA set found the strongest mortality associations with industrial and combustion-related components of the fine aerosol, but not with soil-derived particles. Thus, these analyses suggest that sulfate and associated fine combustion-related particles were most closely associated with mortality.

The Ozkaynak and Thurston (1987) results noted above for analysis of 1980 U.S. mortality provide an interesting overall contrast to the findings of Lipfert (1984) for 1969 to 1970 U.S. mortality data, and to the findings of Lipfert et al. (1988) for the 1980 U.S. mortality data. In particular, whereas Lipfert found TSP coefficients to be most consistently statistically significant (although varying widely depending upon model specifications, explanatory variables included, etc.), Ozkaynak and Thurston (1987) found particle mass measures, including coarse particles (TSP, IP), often to be nonsignificant predictors of total mortality. Also, whereas Lipfert found the sulfate coefficients to be even more unstable than the TSP associations with mortality (and questioned the credibility of the sulfate coefficients), Ozkaynak and Thurston (1987) found that particle exposure measures related to the respirable or toxic fraction of the aerosols (e.g., FP or

sulfates) to be most consistently and significantly associated with annual cross-sectional mortality rates. They estimated a range of particulate matter-total mortality mean effects of 4 to 9% of total U.S. mortality, when sulfates were used as the PM metric. When Lipfert (1988) conducted a reanalysis of the 1980 cross-sectional dataset, and added many more controllers for confounding (e.g., for smoking, water hardness and sulfate artifact), he also reports a significant sulfate coefficient having an elasticity of 2.8 to 13%, which is not statistically different from that reported by Ozkaynak and Thurston (see Lipfert and Morris, 1991, and; Thurston and Ozkaynak, 1992 for discussion). Thus, while results vary somewhat across studies, most cross-sectional analyses of the 1960, 1970, and 1980 data found an association between some measure of chronic PM exposure and increased human mortality. The degree to which sulfate is identified depends on the model specification used in the analysis.

Taken as a whole, these various analyses are usually, but not always, indicative of mortality and morbidity associations with the sulfate fraction of fine particles found in contemporary American urban airsheds. Variations in the acidity of the sulfate fraction may explain this apparent variability in sulfate toxicity. However, without nationwide measurements of airborne acidity, it is difficult to evaluate the relative contribution of acid aerosols within these fine particle sulfates to the reported health effects.

12.5.4.3 Studies Relating Chronic Health Effects to Acid Aerosols

In an hypothesis generating discussion, Speizer (1989) presented city-specific bronchitis prevalence rates from the six cities. While no direct aerosol acidity measurements were made during or before the 1980/81 school year (when the children were examined), Speizer (1989) used pollution data that Spengler et al. (1989) gathered in Kingston/Harriman and St. Louis from December 1985 through September 1986 and in Steubenville and Portage from November 1986 to early September 1987. His plot of bronchitis prevalence as a function of PM_{15} is presented in Figure 12-15. Additional H^+ concentration data from Watertown, MA and Topeka, KS have since been published by Dockery (1993), and all these data are included in the updated version of Speizer's H^+ plot presented in Figure 12-16. It should be noted that these points may contain unaddressed bronchitis variation due to factors other than pollution. For example, illness and hospitalization rates are known to vary across areas, independent of health status factors (Wennberg, 1987; McPherson et al., 1982). Thus, the relationship of bronchitis rates with pollution in these preliminary analyses must be considered as being only suggestive. However, as seen in these figures, when the city-specific bronchitis rates are plotted against mean H^+ concentrations, instead of PM_{15}, there is a relative shift in the ordering of the cities which suggests a better correlation of bronchitis prevalence with H^+ than with PM_{15}.

Damokosh et al. (1993) and later Dockery et al. (1996) report analyses of the 6-City children's bronchitis data more thoroughly by incorporating controls for confounding variables, and by addin a seventh locale, Kanahwa County, WV to the analysis. In that county, PM_{10}, $PM_{2.5}$, and H^+ were measured from 1987 to 1988 during the collection of data on the respiratory health status of 7,910 children in third through fifth grade. As in the 6-City study, respiratory health status was assessed in Kanahwa County via a parent completed questionnaire. Nine indicators of asthmatic and bronchitic symptom reports were considered. A two-stage logistic regression analysis was used, adjusting for maternal

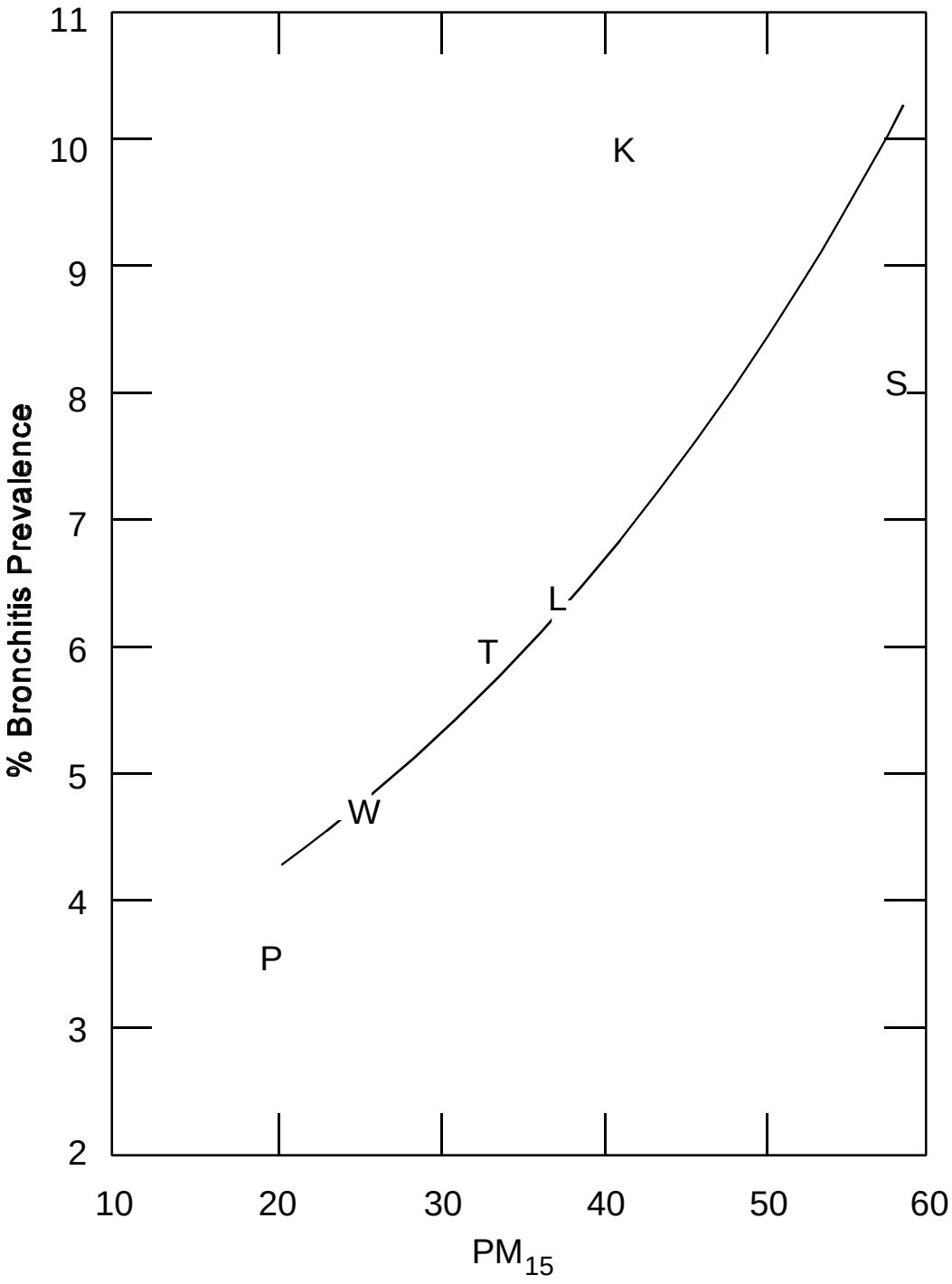

Figure 12-15. Bronchitis in the last year, children 10 to 12 years of age in Six Cities, by PM_{15} (P = Portage, WI; T = Topeka, KS; W = Watertown, MA; K = Kingston, TN; L = St. Louis, MO; S = Steubenville, OH.)

Source: Speizer (1989).

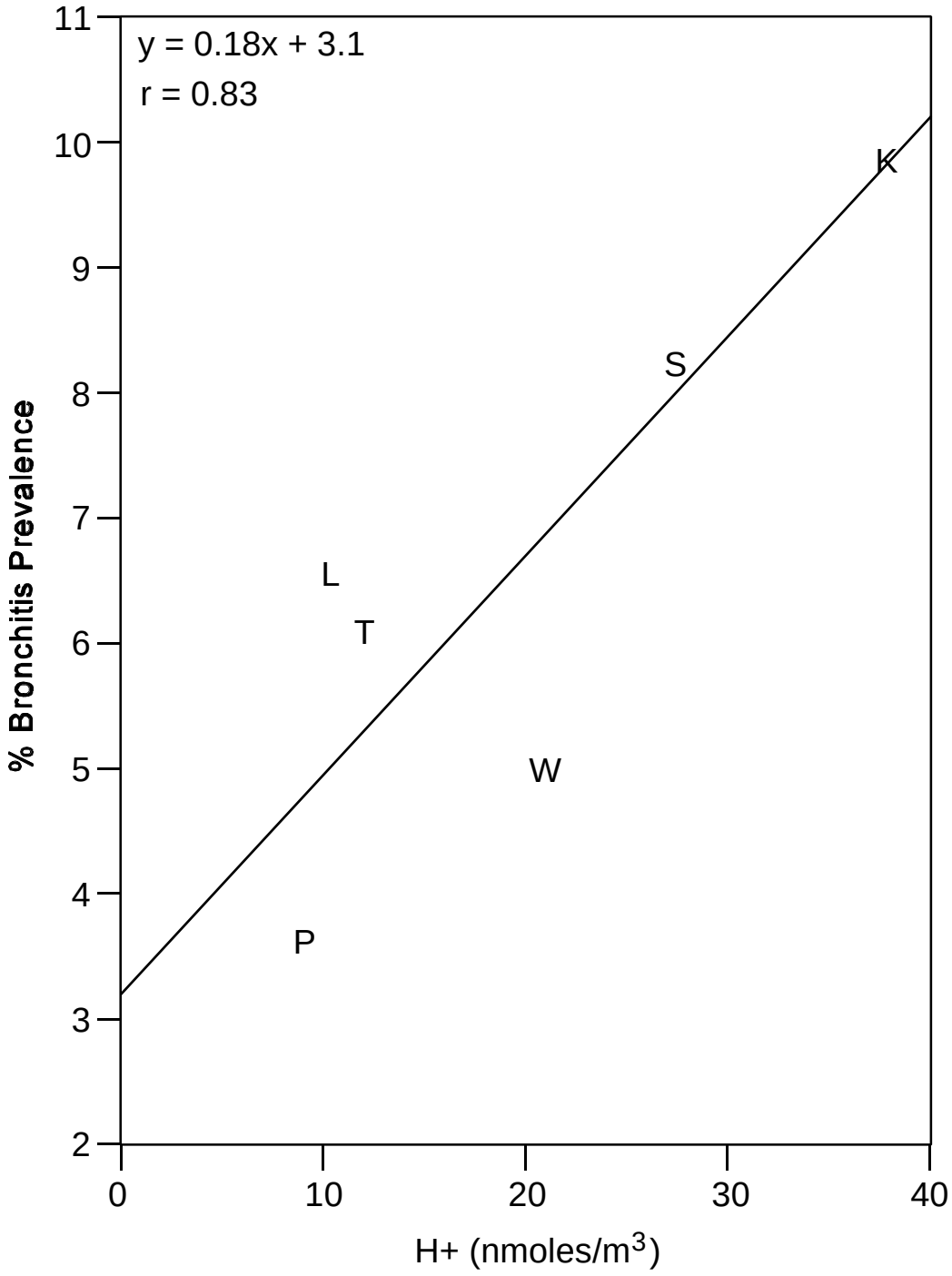

Figure 12-16. Bronchitis in the last year, children 10 to 12 years of age in six U.S. cities, by hydrogen ion concentration. (K = Kingston, TN; L = St. Louis, P = Portage, WI; S = Steubenville, OH; T = Topeka, KS; W = Watertown, MA.)

Source: Dockery (1993); Speizer (1989).

smoking and education, race, and any unexplained variation in symptom rates between the cities. Significant associations were found between summer mean H^+ and chronic bronchitis and related symptoms (cough, phlegm, and chest illness). The estimated relative odds for bronchitic symptoms associated with the lowest mean value of particle strong acidity (15.7 nmoles/m^3) to the highest (57.8 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). No associations were found for asthma or asthma related symptoms (doctor diagnosed asthma, chronic wheeze, and wheeze with attacks of shortness of breath). However, equivalent results were found with other particle mass measurements highly correlated with aerosol acidity.

As a follow-up to the 6-City study, the relationship of respiratory symptom/illness reporting with chronic exposures to acidic aerosols was tested among a cohort of schoolchildren in 24 rural and suburban communities in the United States and Canada (Dockery et al., 1996). Ambient air pollution concentrations were measured for one year in each community. Annual mean particulate strong acidity concentrations ranged from 0.5 to 52 nmoles/m^3 across the 24 communities. Questionnaires were completed by the parents of 15,523 schoolchildren 8 to 12 years of age. Both bronchitic symptoms, (reports of bronchitis, cough, or phlegm) and asthmatic symptoms, (reports of asthma, shortness of breath with wheeze) or persistent wheeze, were considered separately. City-specific reporting rates were first calculated after adjustment for the effects of gender, age, parental asthma, parental education, and parental allergies. Associations with ambient air pollution were then evaluated. Bronchitic symptoms were associated with particulate strong acidity: relative odds 1.66 (95% CI: 1.11 to 2.48) across the range of exposures. Increased reporting of bronchial symptoms were also associated with other measures of particulate air pollution including sulfate - relative odds 1.65 (95% CI: 1.12 to 2.42). However, associations of asthmatic symptom reports with any of the air pollutants, including particulate acidity, were not statistically significant. Stratified analyses did not show any evidence that asthmatics or other potentially sensitive groups of children had a greater response to particulate acidity.

Raizenne et al. (1996) drew upon the same cohort of children described above to specifically examine the health effects in children of living in regions having periods of elevated ambient acidic air pollution (22 communities in the U.S. and Canada, 8 sites/year, 3 years) . Parents of children 8 to 12 years old completed a questionnaire and provided consent for their child to perform a

standardized forced expiratory maneuver on one occasion between October and May. Air and meteorological monitoring were performed in each community for the year preceding the pulmonary function tests. The annual mean particle strong acidity (H^+) ranged from 0.5 to 52 nmoles/m^3, PM_{10} from 18 to 35 µg/m^3, and $PM_{2.1}$ from 6 to 21 µg/m^3. Annual H^+ was more highly correlated with $PM_{2.1}$ (r = .72) and SO_4 (r = .91) than with PM_{10} (r = 0.29). FVC and FEV_1 measurements of 10,251 Caucasian children in 22 communities were used in a two-stage logistic regression analysis, adjusted for age, sex, height, weight, sex-height interaction and parental history of asthma. The reported effect estimates were expressed in terms of 52 nmoles/m^3 difference in H^+. The results indicated that residing in high particle strong acidity regions was associated, on average, with a 3.45% (95% CI 4.87, 2.01) and a 3.11% (95% CI 4.62, 1.58) lower than predicted FVC and $FEV_{1.0}$, respectively. For children with a measured FVC less than or equal to 85% of predicted, the odds ratio for lower lung function was 2.5 (95% CI 1.8, 3.6) across the range of H^+ exposures. Assuming that these exposures reflect lifetime exposure of the children in this study, the data suggest that long-term exposure to ambient particle acidity may have a deleterious effect on normal lung growth, development, and function.

As discussed in detail earlier in this chapter, Dockery et al. (1993) reported results of a prospective cohort study that examined the effects of air pollution on mortality, controlling for individual risk factors. Survival analysis, including Cox proportional-hazards regression modeling, was conducted with data from a 14 to 16 year mortality follow-up of 8,111 adults in six U.S. cities. After adjusting for smoking and other risk factors, statistically significant associations were found between air pollution and mortality. Using inhalable particles, fine particles, or sulfates as the indicator of pollution all gave similar results: an adjusted mortality-rate ratio for the most polluted city as compared to the least polluted city of 1.26 (95% CI = 1.08 to 1.47). Weaker mortality associations were found with H^+ in this analysis. However, the H^+ data employed may not be appropriate for such an analysis. Of the pollutant data considered, the H^+ was the most limited; less than one year of H^+ data collected in each city near the end of the study were used to characterize lifetime exposures of adult study participants. This seems especially inappropriate in Steubenville, OH where the industrial (e.g., steel mill) pollution levels diminished during the course of the study, as the steel industry in the valley declined. Indeed, in Steubenville, the H^+ data were only collected from mid-October, 1986 through early September, 1987

(Spengler et al., 1989). In contrast, the inhalable particle, fine particle, and sulfate data used for each city were more representative, having been collected earlier and over a five to six year period. Thus, not finding a statistically significant correlation between H^+ and mortality (relative to sulfates and fine particles) may be due in large part to the fact that the limited H^+ data employed were not sufficient for this application.

12.5.4.4 Chronic Exposure Effects in Occupational Studies

The last remaining type of information considered here concerns the effects of chronic exposures to acid aerosols in occupational settings. Such studies are discussed mainly in order to provide some perspective on the variety of health effects associated with acid aerosol exposures, albeit at extremely high concentrations not likely to occur in ambient air.

Gamble et al. (1984a) studied pulmonary function and respiratory symptoms in 225 workers in five lead battery acid plants. This acute effect study obtained personal samples of H_2SO_4 taken over the shift. Most personal samples were less than 1 mg/m^3 H_2SO_4, and mass median aerodynamic diameter of H_2SO_4 averaged about 5 μm. The authors concluded that exposure to sulfuric acid mist at these plants showed no significant association with symptoms or acute effects on pulmonary function. The ability of the body to neutralize acidity of H_2SO_4 was considered as one factor in this outcome. Also, the authors speculated that tolerance to H_2SO_4 may develop in habitually exposed workers.

In a related study of chronic effects of sulfuric acid on the respiratory system and teeth, Gamble et al. (1984b) measured in the same workers respiratory symptoms, pulmonary function, chest radiographs, and tooth erosion. Concentrations of H_2SO_4 at the time of the study were usually 1 mg/m^3 or less. Exposures to such acid mist levels showed no significant association with cough, phlegm, dyspnea, wheezing, most measures of pulmonary function, and abnormal chest radiographs. Tooth etching and erosion were strongly related to acid exposure. The authors noted that the absence of a marked effect of acid exposure on respiratory symptoms and pulmonary function may be due to the size of the acid particles, ranging in the 5 plants from 2.6 to 10 μm, MMAD which is much larger than typically <1.0 μm) ambient H^+ aerosols. Moreover, the relative humidity of the lung may cause at least a doubling of particle size, especially in the lower size range. Thus, most acid particles may be deposited in the upper respiratory tract and

many may not even reach the lung. Finally, the authors note that the lack of any convincing finding in this study related to acute respiratory symptoms is not completely unexpected, due to the relatively low exposure (<1 mg/m^3) compared to previous occupational studies.

Williams (1970) studied sickness absence and ventilatory capacity of workers exposed to high concentrations of sulfuric acid mist in the forming department of a battery factory (location not stated). Based on 38 observations made on two days, the forming department had a mean H_2SO_4 concentration of 1.4 mg/m^3, ranging from a trace to 6.1 $\mu g/m^3$. In a different forming department, the mass median diameter of the acid particles was 14 µm. Compared with control groups, men exposed to the high concentrations of sulfuric acid mist in the forming department had slight increases in respiratory disease, particularly bronchitis. There was no evidence of increased lower respiratory disease, which might be explained by the large particle size. After adjusting for circadian variations, there was no evidence of decreased ventilatory function.

Beaumont et al. (1987) studied mortality patterns in 1,165 workers exposed to sulfuric acid and other acid mists in steel-pickling operations. Workplace monitoring during the 1970's indicated worker personal exposures to average 190 $\mu g/m^3$ H_2SO_4. However, as discussed for battery plant operations, the particle size of these mists tend to be larger than ambient acid aerosols, so not all is likely to be respirable. Standardized mortality ratio (SMR) analysis of the full "any acid exposure" cohort (n = 1,165), with the use of U.S. death rates as a standard, showed that lung cancer was significantly elevated, with a mortality ratio of 1.64 (95%CI = 1.14 to 2.28, based on 35 observed deaths). The lung cancer mortality ratio for workers exposed only to sulfuric acid (n = 722) was lower (SMR = 1.39), but further restriction to the time 20 years and more from first employment in a job with probably daily sulfuric acid exposure (~0.2 mg/m^3) yielded a mortality ratio of 1.93 (95% CI = 1.10 to 3.13). An excess lung cancer risk was also seen in workers exposed to acids other than sulfuric acid (SMR = 2.24; 95% CI = 1.02 to 2.46). When comparison was made to other steel workers (rather than to the U.S. general population) to control for socio-economic and life-style factors such as smoking, the largest lung cancer excess was again seen in workers exposed to acids other than sulfuric acid (SMR = 2.00; 95% CI = 1.06 to 3.78). However, the smaller rate ratios may have been partly due to the restriction of this sub-analysis to white males, which excluded the higher excess lung cancer risk in nonwhite males. Adjustment for potential differences in smoking habits showed that increased smoking was

unlikely to have entirely explained the increased risk. Mortality from causes of death other than lung cancer was unremarkable, with the exception of significantly lower rates for deaths due to digestive system diseases. These results suggest that chronic acid aerosol exposures may promote lung cancer at high concentrations, perhaps via chronic irritation of respiratory tissues, or by some other mechanism (e.g., by affecting clearance rates in the lung).

12.5.5 Summary of Studies on Acid Aerosols

Historical and present-day evidence suggest that there can be both acute and chronic effects by strongly acidic PM on human health. Evidence from historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations (on the order of 400 $\mu g/m^3$ as H_2SO_4, or roughly 8,000 nmoles/m^3 H^+) may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and SO_2. In addition, Thurston et al. (1989) and Ito et al. (1993) both found significant associations between acid aerosols and mortality in London during non-episode pollution levels (30 $\mu g/m^3$ as H_2SO_4, or approximately 600 nmoles/m^3 H^+), though these associations could not be separated from those for BS or SO_2. The only attempts to date to associate present-day levels of acidic aerosols with acute and chronic mortality (Dockery et al., 1992; Dockery et al., 1993, Schwartz et al., 1996) failed to do so, but there may not have been a sufficiently long series of H^+ data to detect H^+ associations. In recently reported Utah Valley, PM_{10} studies (Pope et al. 1991, 1992), PM_{10}-health effects association were found, despite limited H^+ sampling indicating low acid aerosol levels. This is not inconsistent with adverse health effects from H^+, however, when it is considered that PM can contain numerous toxic agents other than H^+. There is a critical need for present day replications of the extensive London mortality-acid aerosol studies to be conducted, however, in order to determine if the London wintertime health effects associations (which occurred predominantly in wintertime reduction-type atmospheres) are pertinent to present-day U.S. conditions, in which acid aerosol peaks occur primarily in the summer months (in oxidation-type atmospheres).

Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has now been observed under present-day conditions, as well. Thurston et al. (1992) and Thurston et al. (1994b) have noted associations

between ambient acidic aerosols and summertime respiratory hospital admissions in both New York State and Toronto, Canada, respectively, even after controlling for potentially confounding temperature effects. In the latter of these studies, significant independent H^+ effects remained even after simultaneously considering the other major co-pollutant, O_3, in the regression model. While the New York State study considered only ozone as a possible confounder, the Toronto study also considered NO_2 and SO_2, but found them to be non-significant. In the Toronto analysis, the increase in respiratory hospital admissions associated with H^+ was indicated to be roughly six times that for non-acidic PM_{10} (per unit mass). In these studies, H^+ effects were estimated to be the largest during acid aerosol episodes (H^+ 10 $\mu g/m^3$ as H_2SO_4, or 200 nmoles/m_3 H^+), which occur roughly 2 to 3 times per year in eastern North America. These studies provide evidence that present-day strongly acidic aerosols can represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic PM effects in this population. While the 6-City study of diaries kept by parents of children's respiratory and other illness did not demonstrate H^+ associations with lower respiratory symptoms except at H^+ above 110 moles/m_3 (Schwartz et al., 1994), upper respiratory symptoms in two of the cities were found to be most strongly associated with daily measurements of H_2SO_4 (Schwartz, et al., 1991b). Some, but not all, recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O_3 (Studnicka et al., 1995; Neas et al., 1995).

Studies of the effects of chronic H^+ exposures on children's respiratory health and lung function are generally consistent with effects as a result of chronic H^+ exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H^+ concentrations than with PM in general (Speizer, 1989). A follow-up analysis of these cities and a seventh locality which controlled the analysis for maternal smoking and education and for race, suggested associations between summertime average H^+ and chronic bronchitic and related symptoms (Damokosh et al., 1993; Dockery et al., 1996). The relative odds of bronchitic symptoms with the highest acid concentration (58

nmoles/m^3 H^+) versus the lowest concentration (16 nmoles/m^3) was 2.4 (95% CI: 1.9 to 3.2). Furthermore, in a follow-up study of children in 24 U.S. and Canadian communities (Dockery et al., 1996) in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (relative odds = 1.66, 95% CI: 1.11 to 2.48). It was also found that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity (Raizenne et al., 1996). Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children.

12.6 DISCUSSION

12.6.1 Introduction and Basis for Study Evaluation

The epidemiologic studies of human health effects related to PM exposure play a particularly important role because there is somewhat less supporting information on exposure-response information from toxicological or clinical studies compared to other criteria pollutants. We have therefore paid special attention to methodological issues in the studies that have been reviewed in this epidemiology chapter. Various health endpoints have been used in these studies, including respiratory function measures, respiratory symptom reports, hospital admissions, total non-accidental mortality, and mortality classified by medical cause of death such as respiratory or cardiovascular classifications. Each health outcome has many causes other than air pollution, and no specific air pollutant can be uniquely associated with a specific outcome, including PM and its components. Subject-specific (personal) exposure to PM or to other air pollutants is unmeasured in almost all of the studies, and exposure to PM, to other pollutants, or even to weather variables, is only estimated from one or a few monitoring sites in a large metropolitan area or region. Demographic information can be used with either longitudinal studies, prospective studies, or cross-sectional studies, but age is the only individual subject variable that has been used in almost all studies. Other personal variables can be obtained in prospective studies. Comparisons across different cities must be adjusted for demographic and climatologic differences, and usually are in cross-sectional studies. Studies of acute responses to air pollutants, whether measured by

respiratory function indices, respiratory symptoms, hospital admissions, or mortality, have been compared by various formal or informal meta-analytic techniques (Schwartz, 1992a, 1994c; Dockery and Pope, 1994b), but there has so far been no effort to adjust the results of the metaanalyses for quantitative differences among study groups or for differences in data-analytic methodologies.

Many of the differences in results cannot reasonably be attributed to differences in methods of data analysis. Very similar estimates of the effects of PM can be obtained for a wide range of alternative data analysis methods. Ideally, models for short-term effects should be adjusted for seasonality, for long-term and transient irregular events such as influenza epidemics, for auto- and cross-correlation structure when necessary, for sensitivity to distributional assumptions such as Poisson or hyper-Poisson variability and, if not based on demonstrably robust methods, for sensitivity to unusual values among either predictor or response data. Models used in the individual studies in EPA meta analyses, have generally met most of these criteria.

12.6.1.1 Differences Among Study Results

What is more disturbing is that, using similar data sets, different investigators of acute mortality effects have derived different estimates of PM effect size or statistical significance. There are at least two possible reasons for this. The first is that there may be some genuine confounders of PM effects on human health. In some studies, under some meteorological or seasonal conditions, co-pollutants will be emitted by some of the same sources as emit PM, so that there will be a close intrinsic relationship between PM and some other pollutants. This may also extend to certain meteorological variables, which may be related both to atmospheric dispersion of all outdoor pollutants and to pollutant emissions rates. For example, an extremely hot day in summer may be associated with increased use of electrical power for air conditioning (increasing emissions of PM and other pollutants such as SO_2 from local electricity generating plants that burn fossil fuels) and, also, with increased motor vehicle use as people travel to less uncomfortable locations (increasing vehicle-generated pollutants from gasoline and other motor vehicle fuels, including O_3, CO, and NO_2). Primary gaseous pollutants may become secondary atmospheric sources of certain PM components, such as sulfates and nitrates. While there are a number of statistical diagnostics for intrinsic confounding, and even a few adequate methods for

partially resolving seriously confounded predictors of response, these have rarely been used. Analyses in which only a single pollutant is used to predict a health effect are not wholly satisfactory without confirmation by multi-pollutant analyses, adjusted for confounding insofar as possible. In this regard, comparison across different studies, including those in which each potentially confounding factor is or is not present, may be needed to assess the effects of PM in the absence of detailed technical assessments of sensitivity to intrinsically confounded variables.

The second reason why different investigators may derive different results for acute mortality is much more profound. In the absence of generally acceptable mechanistic relationships among potentially confounding variables, and in the absence of generally acceptable specifications for the exposure-response relationships for PM, for co-pollutants, and for weather, all modelling is data-driven and empirical. This has led almost all investigators into extensive model specification searches, in which numerous alternative models may be fitted to the same data or to subsets of the same data set until a "best fitting" or "statistically significant" model is obtained. It has long been known (Leamer, 1978) that data-driven model specification searches can seriously distort the actual significance level of the regression coefficients in ordinary linear regression models with independent Gaussian errors, and by extension we expect the same problem in Poisson and hyper-Poisson exponential regression models with complicated correlation structures. This is similar to the better-known "multiple comparisons" problem, in which all possible subsets of a set of hypothesis tests in a linear analysis of (co)variance could be tested, with a corresponding artificial inflation of the statistical significance of the whole ensemble of tests. However, the complicated model specification searches that have produced the models reported in the published PM epidemiologic studies have a hypothetically limitless number of alternative specifications.

In evaluating model specification options, a model specification search may be extended until some combination of correlation model or lag structure, adjustments for time trends, season, co-pollutants, and weather produces a model in which the study response data are fitted well and the PM coefficient is "statistically significant". Statistical significance for a PM coefficient means that either an asymptotic confidence interval or a more exact likelihood ratio-based confidence interval for the effect does not cover the null value (0 for effect size, 1 for relative risk). Or, the specification search may proceed towards the goal of establishing that some other pollutant in the

model is a statistically significant predictor of changes in mortality rates or hospital admission rates (etc.) or that some combination of meteorological variables can fit the observed health effects data when the PM coefficient is not statistically significant. This could provide the basis of an argument that some factor(s) other than PM are accounting for the observed effects. Because of the confounding that exists between PM and other variables that may be used in the models, there may be many substantial points of similarity between the models with a significant PM effect and those without a significant PM effect, at least in some cities during some years. There may thus be little internal basis for choosing between two models, one with a significant PM effect and another, using similar specifications in many ways, without a significant PM effect.

There are several ways in which the indeterminacy of the models from different studies of the same data set could be resolved. The first method, and in many ways the best, is to see which of the competing models does the best job of predicting new information. Since new information is not readily at hand, a more realistic method would be "internal cross-validation". The model would be fitted to one subset of the data and then the parameters derived from the model based on one part of the data would be used to predict the other part. In time series analysis, the use of the first part of the series to predict the last part of the series is known as "postdiction", to distinguish the exercise from a genuine forecast or prediction in which the future observations and their predictors are in fact unknown. A related approach would be to use the PM and co-pollutant models derived from one group of cities to estimate health effects in another group of cities, where "pre-models" specific to each of the second group of cities are used to adjust mortality rates for all non-pollution variables such as meteorological variables. In practice, we are not aware of any efforts to assess the predictive validity of any of the models, either in an absolute sense or relative to a competing model.

12.6.1.2 Importance of Comparisons Across Different Cities

We are therefore limited to evaluating models reported in different studies on the basis of comparisons of results for different geographic sites (cities, SMSA's, etc.) or during different periods of time. If the estimated PM effect is similar in magnitude across a range of different cities, differing in location, climate, co-pollutant inventories, demographics, or other relevant factors, we may argue that these effect estimates are relatively robust with respect to exact specifications of different models. This is discussed in more detail in Section 12.6.3.

Similarly, weather is an important confounding factor. Adjustments for meteorological variables may differ substantially from one study to another. It is easier to compare effect size estimates from studies with similar adjustment methods. However, there are likely to be real differences among cities that complicate the use of weather effect models found at one location to adjust for weather effects on human health in another location. This is particularly likely to affect adjustments made for extreme weather conditions, whether defined by a threshold for a temperature effect or by a weather-related synoptic category. It is, in any event, easier to identify a quantitative PM relationship during non-extreme weather conditions, or during non-offensive synoptic categories. Studies in which the size of the PM exposure-response relationship was estimated for non-extreme weather conditions, or for which appropriate adjustments were made in the analysis, are also accorded higher weight than those without such distinctions.

Finally, there is a question about how the effect size estimates in different cities should be combined, or whether there should be a combined estimate. Combined estimates using meta-analytic techniques have been published (Schwartz, 1994c; Dockery and Pope, 1994b), and additional meta-analyses for the more recent studies may be useful. However, there is a possibility that real differences exist among PM effect sizes in different communities. The differences may be due to differences in area-specific PM composition, in sub-populations, in pre-existing health status, in acclimatization to weather conditions, or to effects of other unmeasured air pollutants. If the differences among communities are substantial, it may be preferable to treat the PM effect on health outcome as a random effect across communities, even though the reasons for the differences are potentially explainable, but unknown at present.

12.6.1.3 Sample Size and Power of Reported PM-Mortality Associations

Since the size of the 'relative risks' and the extent of associations found in recent observational studies of PM-mortality are not 'large', such associations are unlikely to be shown in a 'small' sample size (i.e., a limited number of days). This can be particularly problematic if one plans to analyze the data using PM data collected at the current U.S. sampling frequency (i.e., every-6th-day). It should be noted that a majority of the existing studies that reported significant PM-mortality associations used PM data that were collected daily. A determination of the sample size required to find the observed association in a given community is not simple, because power may be dependent on not only sample size, but also on: (1) the population size of the community (to produce certain number of deaths per day); (2) the levels of PM; (3) the proportion of susceptible populations (e.g., age/race/gender distribution); (4) the location and number of PM sampling sites to estimate representative PM exposure of the population, and; (5) the model specification. Also, determining the expected 'effect' size from the published studies alone may be misleading because of potential 'publication bias' towards significant effects. With this caveat in mind, one can illustrate the effects of sample size and the above mentioned factors on the significance of PM/total daily mortality associations, by examining the t-ratios of the PM coefficients reported by recent U.S. PM-mortality studies (Table 12-25). When both multi-pollutant models and single pollutant models were presented, a single pollutant model was selected here. All the models included weather variables. When both Poisson models (log-linear GLM) and OLS models were presented (Schwartz, 1993a; Kinney et al., 1995), both gave essentially identical t-ratios, and therefore the results for Poisson models are shown. Despite the magnitude of differences in various studies' population/mean deaths, the key predictor of t-ratio appears to be the number of study days (sample size).

In a simple linear regression, the t-ratio for the null hypothesis of a regression coefficient being zero is a function of square-root of sample size, with its slope being $r/(1-r^2)^{0.5}$, where r is the underlying size of the correlation between the dependent variable (e.g., mortality) and the explanatory variable (e.g., PM). The plot (Figure 12-17) of these t-ratios versus square-root of sample days from Table 12-25 in fact shows the t-ratio's strong linear dependency on the square-root of sample size. The magnitude of PM-mortality associations seen in these studies, as reflected in the slope (r=0.083, if the slope is equated to $r/(1-r^2)^{0.5}$, requires about n=600 days for the association to be significant at 0.05 (two-tailed), or n=400 for one-tailed test at 0.05 level.

The required sample size observations to detect this size of r with 80% power is about 800 days. Therefore, findings of statistical non-significance of PM effect may reflect inadequate power to detect an effect of this magnitude if sample size is limited.

12.6.2 Sensitivity of Particulate Matter Effects to Model Specification in Individual Studies

12.6.2.1 Model Specification for Acute Mortality Studies

Many different statistical models have been used to interpret short-term mortality and morbidity studies. The model specifications and methods used to interpret the long-term studies are generally different from those used in analyzing the short-term studies. It is often difficult to compare estimates of PM effect in different studies when the estimates of effect size are obtained by different methods. Differences in effect size estimates may then occur because of differences in modelling approach as well as any real differences in response to PM exposure.

TABLE 12-25. SAMPLE SIZE, SIGNIFICANCE, AND OTHER CHARACTERISTICS OF RECENT STUDIES ON DAILY PARTICULATE MATTER/MORTALITY IN U.S. CITIES

Area	Period	Sample Size	t-ratio	Population	Daily Number Deaths	PM measure and mean[a]	Lag and Average	Reference
Birmingham, AL	1985-1988	1,087	2.52	884,000	17	PM10; 48	same + 2 prev-day	Schwartz (1993a)
Cincinnati, OH	1977-1982	2,191	3.47	873,224	21	TSP; 76	same-day	Schwartz (1994a)
Cook Co., IL	1985-1990	1,357	3.43	5,300,000	117	PM10; 38	same-day	Ito et al. (1995)
Detroit, MI	1973-1982	3,652	3.76	1,200,000	53	TSP; 87	prev. day	Schwartz (1991a)
Kingston, TN	1985-1986	330	1.07	640,887	16	PM10; 30	prev. day	Dockery et al. (1992)
Los Angeles, CA	1985-1990	364	1.96	8,300,000	153	PM10; 58	same-day	Kinney et al. (1995)
Santa Clara, CA	1980-1986	549	2.86	1,400,000	18	COH; 67	same-day	Fairley (1990)
St. Louis, MO	1985-1986	311	2.17	2,356,460	56	PM10; 28	prev. day	Dockery et al. (1992)
Steubenville, OH	1974-1984	4,016	4.66	163,099	3	TSP; 111	prev. day	Schwartz and Dockery (1992b)
Philadelphia, PA	1973-1980	2,726	5.04	1,688,710	48	TSP; 77	same+prev-day	Schwartz and Dockery (1992a)
Utah Valley, UT	1985-1989	1,706	4.78	260,000	3	PM10; 47	same+4prev-day	Pope et al. (1992)

[a]$\mu g/m^3$, unless otherwise noted
[b]12XCOH, unitless

Note: When multiple models were presented, the model with single pollutant (PM) and weather, season variables for the entire year was chosen.

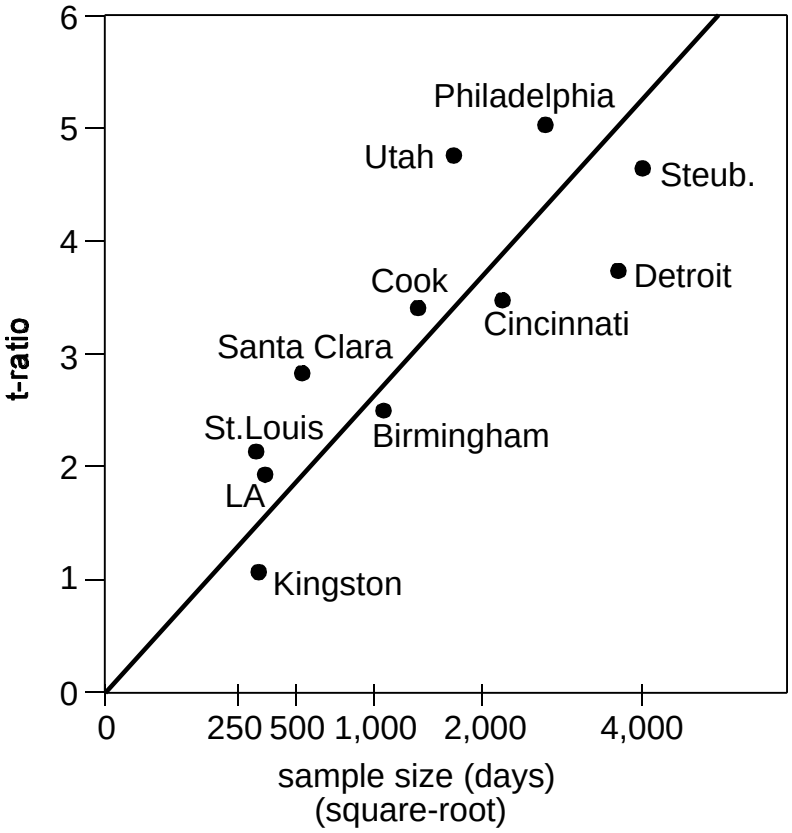

Figure 12-17. t-Ratios of particulate matter coefficients versus sample size (days) from 11 recent U.S. studies.

Many of the papers reviewed in this chapter provide enough information to assess the authors' choice of their "best" model, which we have reported in the summary tables. An extensive discussion of alternative modelling approaches for short-term exposure studies was already evident in earlier papers, such as the analyses of BS in London in the 1960's (Ostro, 1984; Thurston et al., 1989; Schwartz and Marcus, 1990; Ito, 1990), KM in Los Angeles (Shumway et al., 1988; Kinney and Ozkaynak, 1991), and COH in Santa Clara (Fairley, 1990). More recent work has moved in some substantially different directions, recognizing the non-Gaussian nature of discrete data such as daily death counts and hospital admissions, and incorporating a growing variety of data-driven non-parametric or semi-parametric models for PM and other covariates. The more recent studies are discussed below, emphasizing those studies in which PM_{10} or TSP are used as PM indicators.

Model Specification for the Utah Valley Mortality Study (Pope et al., 1992)

One of the most comprehensive assessments of alternative model specifications was presented by Pope in a report presented at the EPA-sponsored workshop on PM-related mortality held in November, 1994 (Pope, 1994). The results of these additional analyses of the Utah Valley study were described briefly in Section 12.3.1 and are presented below graphically, with a view towards resolving model specification issues. For each comparison, a sequence of three graphs is presented that illustrates the results for total (non-accidental) mortality, for death from respiratory causes, and for death from cardiovascular causes. The horizontal bars show the 95 percent confidence limits for relative risk (denoted RR) corresponding to 50 $\mu g/m^3$ in PM_{10}.

Figures 12-18a through 12-18c show the RR estimates for Poisson regression models. The RR for PM quintiles given in the published paper (Pope et al., 1992) is denoted Model 0. The next group, Models 1 through 5, show the results of fitting increasingly adjusted parametric models, from those with only a linear PM_{10} effect (Model 1), and subsequently adding adjustments for time trend (Model 2), temperature (Model 3), humidity (Model 4), and operation of the mill (Model 5) to the preceding model. The relative risk for total mortality (Figure 12-18a) was little affected in Models 1 and 2, but dropped somewhat after temperature was included (Model 3). The relative risk for respiratory mortality (Figure 12-18b) was less affected by temperature, but shifted upward after humidity was added (Model 4). Cardiovascular mortality (Figure 12-18c), like total mortality, also dropped slightly after temperature was added to the model. The relative risk for the next four models (Model 6 through 9) are parallel to Models 2 through 5, except that a non-parametric smoothing function LOESS was used to model time trend, temperature, and humidity respectively in Models 6, 7, and 8; a dummy variable for mill operation was added in Model 9. Model 13 is the same as Model 8 without adjusting for time trend by a LOESS fit on day of the study. In general, RR using at least one LOESS smoother provided a somewhat higher RR for total mortality against PM_{10} in the Utah Valley study, but the difference in RR among these Poisson models is small. RR for respiratory mortality increased as each smoothed covariate was added, but never rose much beyond that for the published model. LOESS smoothers had little effect on RR for cardiovascular mortality.

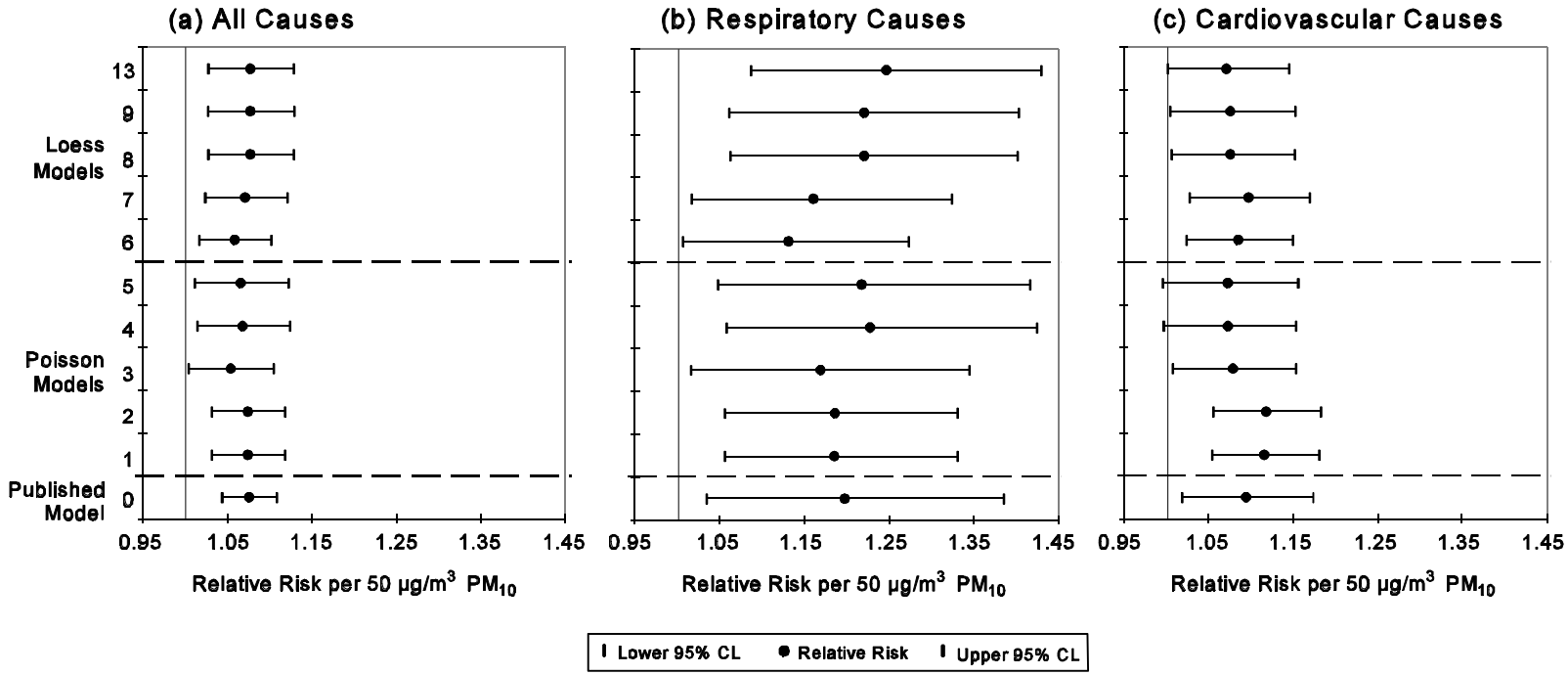

Figure 12-18. Relative risk of mortality for PMin Utah Valley, as a function of several parametric and semiparametric models of time, temperature, and dewpoint: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.

Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).

The next group of model comparisons is shown as Figures 12-19a through 12-19c. These compare several parametric Poisson models with the analogous Gaussian ordinary least squares (OLS) linear models for mortality. Even though the distributional assumptions for a Gaussian distribution fail utterly, the regression coefficients and calculated RR are not very different than the analogous estimates from Poisson regression models.

Figures 12-20a through 12-20c show the effects of separating the annual data into segments, here called "summer" (April to September) and "winter" (October to March). The RR for total mortality (Figure 12-20a), for respiratory mortality (Figure 12-20b), and for cardiovascular mortality (Figure 12-20c) are all statistically significant on an annual basis, while differing substantially in magnitude. Most of this effect is seen to occur from the winter months when the PM_{10} concentrations were highest, whether or not the mill was operating, based on Model 13 in which temperature and humidity effects were adjusted using LOESS smoothing. The relative risk and its estimated uncertainty for all three mortality endpoints is nearly the same using whole year data as when using winter data alone. While PM levels are generally much lower during the summer half of the year than in the winter half, the summer RR estimates are higher than the winter RR estimates, but not significantly different. However, the smaller range of summer PM values results in much larger uncertainty about the summer RR than the winter RR. This illustrates a general problem in subsetting the data by year, season, or month: the increased specificity of RR estimates for subsets of data is usually offset by the loss of precision in the estimates. In general, small increases in uncertainty of subset data RR estimates compared to whole data set RR estimates occur only for the subset(s) of the data that are most influential in establishing the whole data set RR estimate, such as the "winter" subset in this Utah Valley study.

A number of additional reanalyses have recently been presented by Pope and Kalkstein (1996) with results that are almost identical to those shown here. These results demonstrate the relative lack of sensitivity to other methods for weather adjustments, including use of synoptic climatologic categories.

Figures 12-21a through 12-21c extend these Utah analyses to assessing the effect of a co-pollutant, ozone. Including either daily average ozone concentration or maximum one-hour O_3 concentration as predictors of the three mortality endpoints leaves the PM_{10} RR

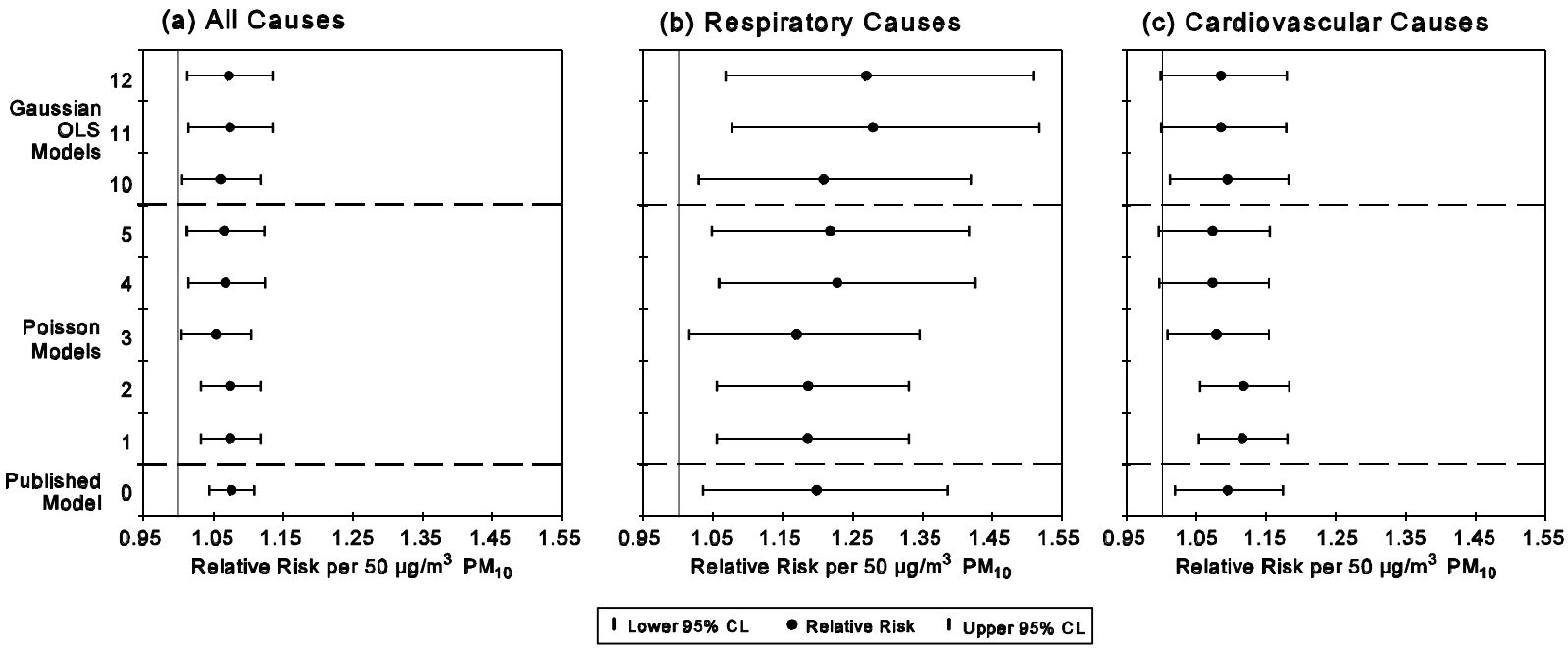

Figure 12-19. Relative risk of mortality for PM_{10} in Utah Valley, as a function of several Poisson and Gaussian regression models of time, temperature and dewpoint: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.

Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).

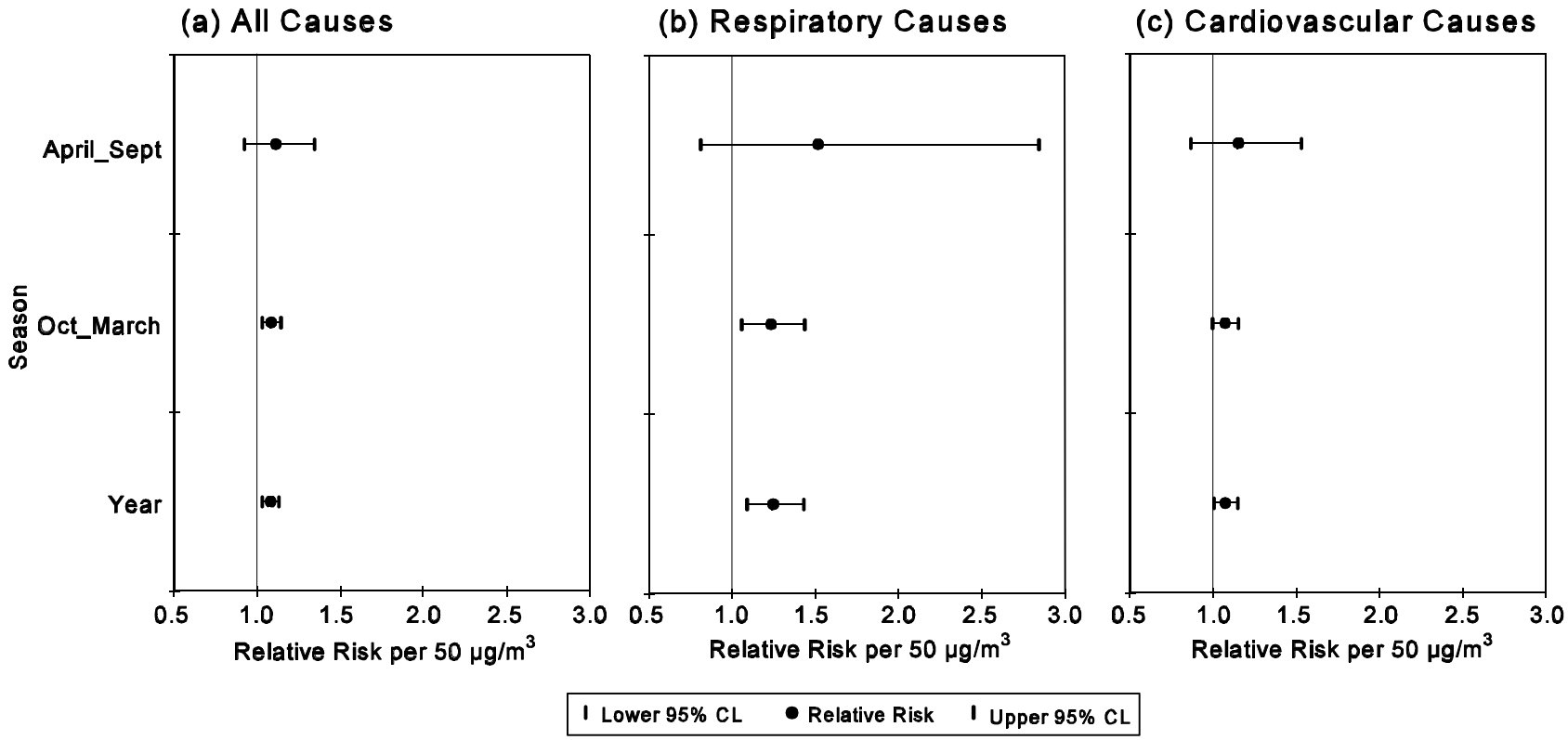

Figure 12-20. Relative risk of mortality for PM_{10} in Utah Valley, as a function of season: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.

Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).

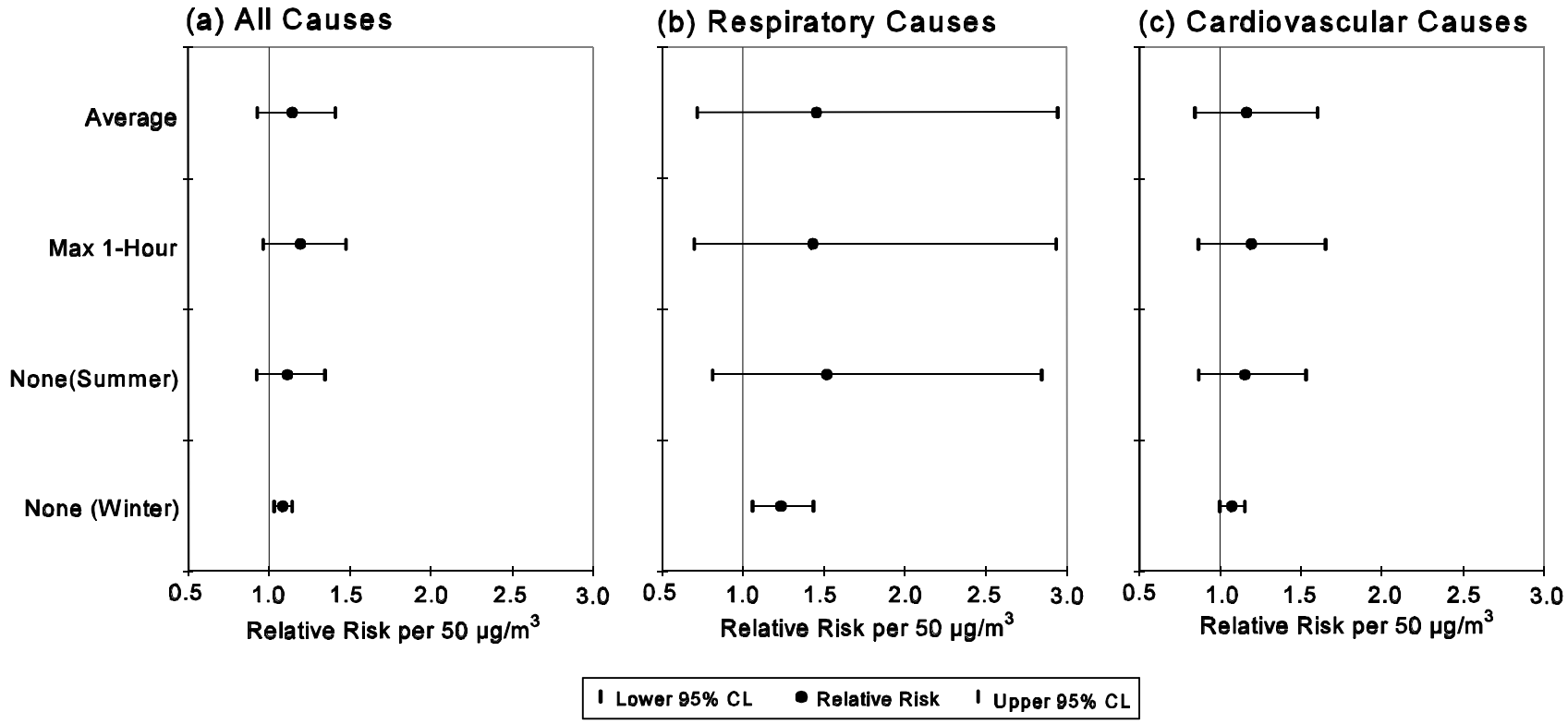

Figure 12-21. Relative risk of mortality for PMin Utah Valley, as a function of ozone indicator in the model: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.

Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).

estimate nearly unchanged from the summer PM_{10} RR estimate obtained without including O_3 as a predictor. Summer RR estimates for all models, with or without O_3, are somewhat larger than the winter or whole-year RR estimate for PM, and have much greater uncertainty. It may be argued that this indicates little confounding of the estimated PM effect with an estimated O_3 effect, and by implication little potential for confounding with other pollutants generated by combustion of fossil fuels by mobile sources, at least in this study.

Figures 12-22a through 12-22c show that specification of PM averaging time may be a critical component of the modelling exercise. Moving averages of 4, 5, or 6 days would provide very similar estimates of a statistically significant PM effect on total mortality (Figure 12-22a) or respiratory mortality (Figure 12-22b). The 5-day moving average used by Pope in most analyses gave the better prediction of cardiovascular mortality (Figure 12-22c).

Model Specification for the Santiago, Chile, Mortality Study (Ostro et al., 1996)

Many model specifications were evaluated in the study by Ostro et al. (1996) discussed in Section 12.3.1. Model specification tests were designed to systematically examine important issues, and results were reported in detail. Figure 12-23 depicts the results graphically. Figure 12-23a shows the RR estimates and large-sample confidence intervals for 10 different Poisson regression models. Figure 12-23a shows the RR values in Table 3 of the Ostro et al. (1996) paper calculated to a base of 115ug/m^3 for models that are linear in average or maximum PM_{10}, or for a change from 115 to 230 ug/m^3 for their logarithms. Inclusion of temperature-related variables reduced RR slightly, from about 1.16 to about 1.10. Inclusion of additional dummy variables for year, quarter, and day of week had little effect on RR, but adding variables for quarter and month reduced RR to about 1.05, which was still statistically significant. Figure 12-23a also shows the results of additional sensitivity tests controlling seasonality in a variety of different ways. The results are somewhat parallel to those of the Utah Valley study discussed above, but with somewhat smaller values. Summer and winter coefficients were very similar, but the RR effect was not quite statistically significant in summer using a two-tailed test with alpha = 0.05. All other model specifications showed a significant PM_{10} effect. The RR of the effect increased somewhat

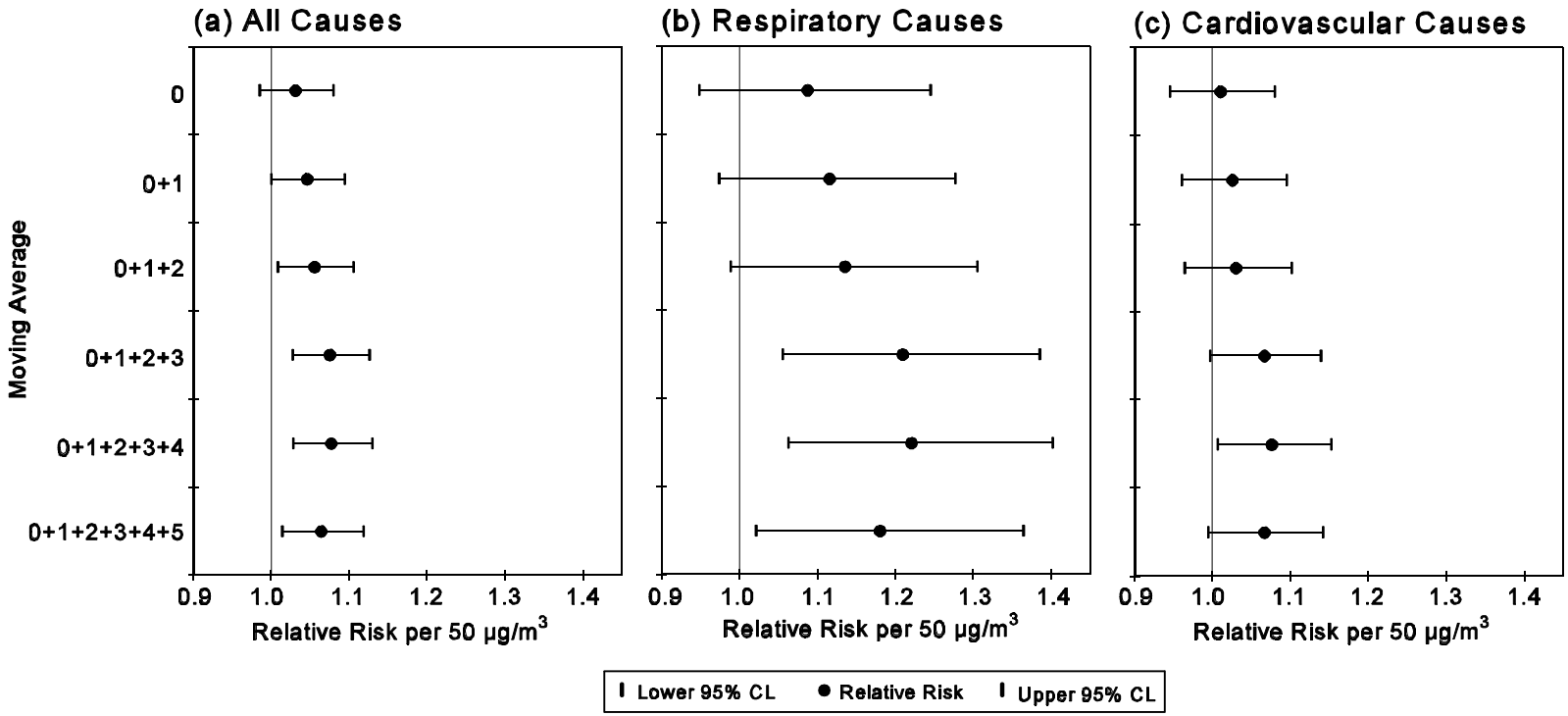

Figure 12-22. Relative risk of mortality for PM_{10} in Utah Valley, as a function of the moving average model: (a) all causes, (b) respiratory causes, and (c) cardiovascular causes.

Source: U.S. EPA graphical depiction of results from Pope et al. (1992) and Pope (1994).

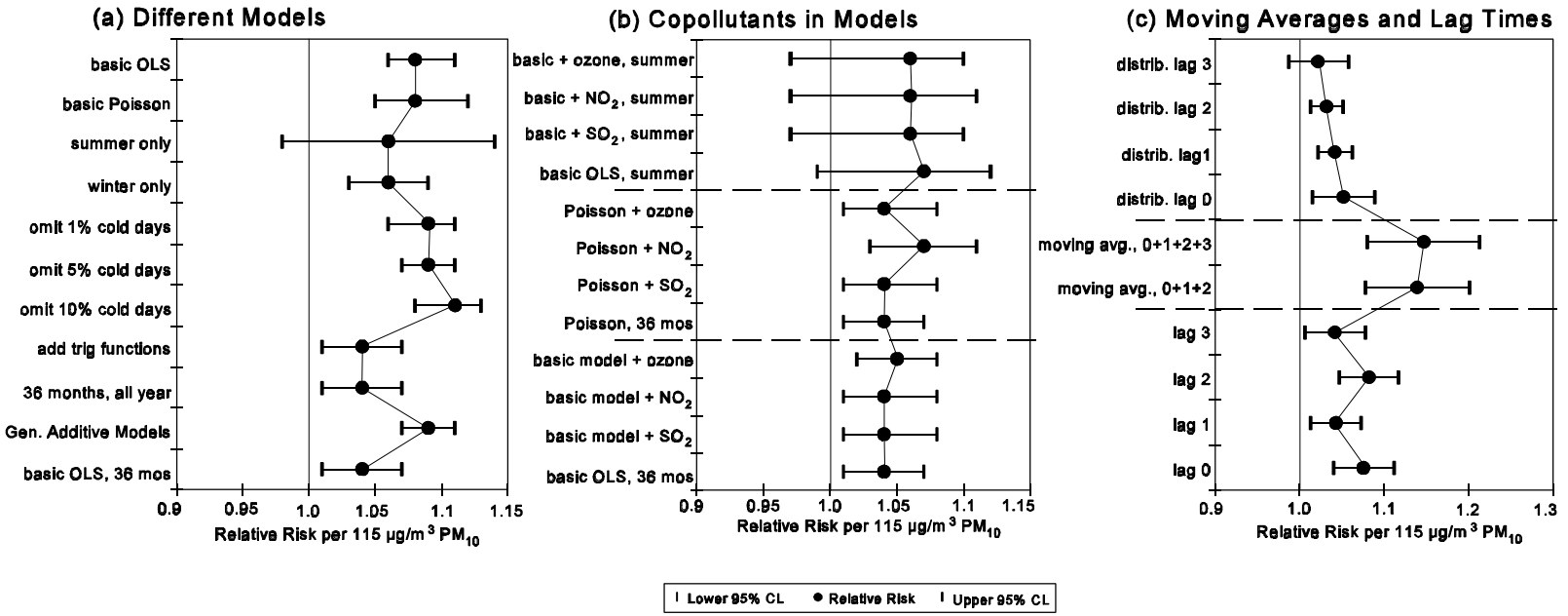

Figure 12-23. Relative risk of total mortality for PM_{10} in Santiago, Chile, as a function of (a) different models, (b) models for co-pollutants, and (c) moving averages and lag times.

Source: U.S. EPA graphical depiction of results from Ostro et al. (1996).

when the coldest days were omitted. Including additional trigonometric terms, or including 36 dummy variables for combinations of year and month reduced the RR for PM, but did not eliminate PM as a significant contributor to total mortality. Control of seasonality by use of a generalized additive model to adjust for time effects gave a somewhat larger RR for PM_{10}, with small uncertainty. Figure 12-23b shows that the estimated TSP effect has little sensitivity to the inclusion of copollutants: NO_2, SO_2, O_3.

Figure 12-23c evaluates a number of lag and moving average models for PM. The relative risks corresponding to each term have been recalculated from the regression coefficients (denoted b) in their Table 8, for a basis of 100 to 150 $\mu g/m^3$, by the formula

$$RR = \exp(b * \log(150/100)),$$

with confidence limits estimated analogously. All of the PM effects are statistically significant, with the exception of the 3-day lag term in the 4-day polynomial distributed lag (PDL) model. The 0-day and 2-day single lag models and the 3-day and 4-day moving average models perform almost as well at predicting total mortality as does the PDL model, of which they are each a special case.

Model Specification for the St. Louis and Eastern Tennessee Mortality Studies (Dockery et al., 1992)

The daily mortality data for St. Louis and for eastern Tennessee analyzed by Dockery et al. (1992) were discussed in Section 12.3.1. Additional results contributing to the analysis were presented by Dockery in a report presented at the EPA-sponsored workshop on PM-related mortality in November, 1994 (Dockery, 1995). Figure 12-24a,b illustrates the sensitivity of the PM_{10} RR to the lag time or moving average model in the Poisson regression for St. Louis total mortality, and Figure 12-25a,b shows the analogous plot for the eastern Tennessee area. Models were fitted for lags from 0 to 4 days, and for the lagged moving average from the two preceding days. The lag 1 and 2 RR estimates for St. Louis, and the lagged 2-day moving average were statistically significant for the St. Louis mortality series, but no PM indicator had a statistically significant RR for PM_{10} in the eastern Tennessee mortality series even though the RR estimates were numerically very similar.

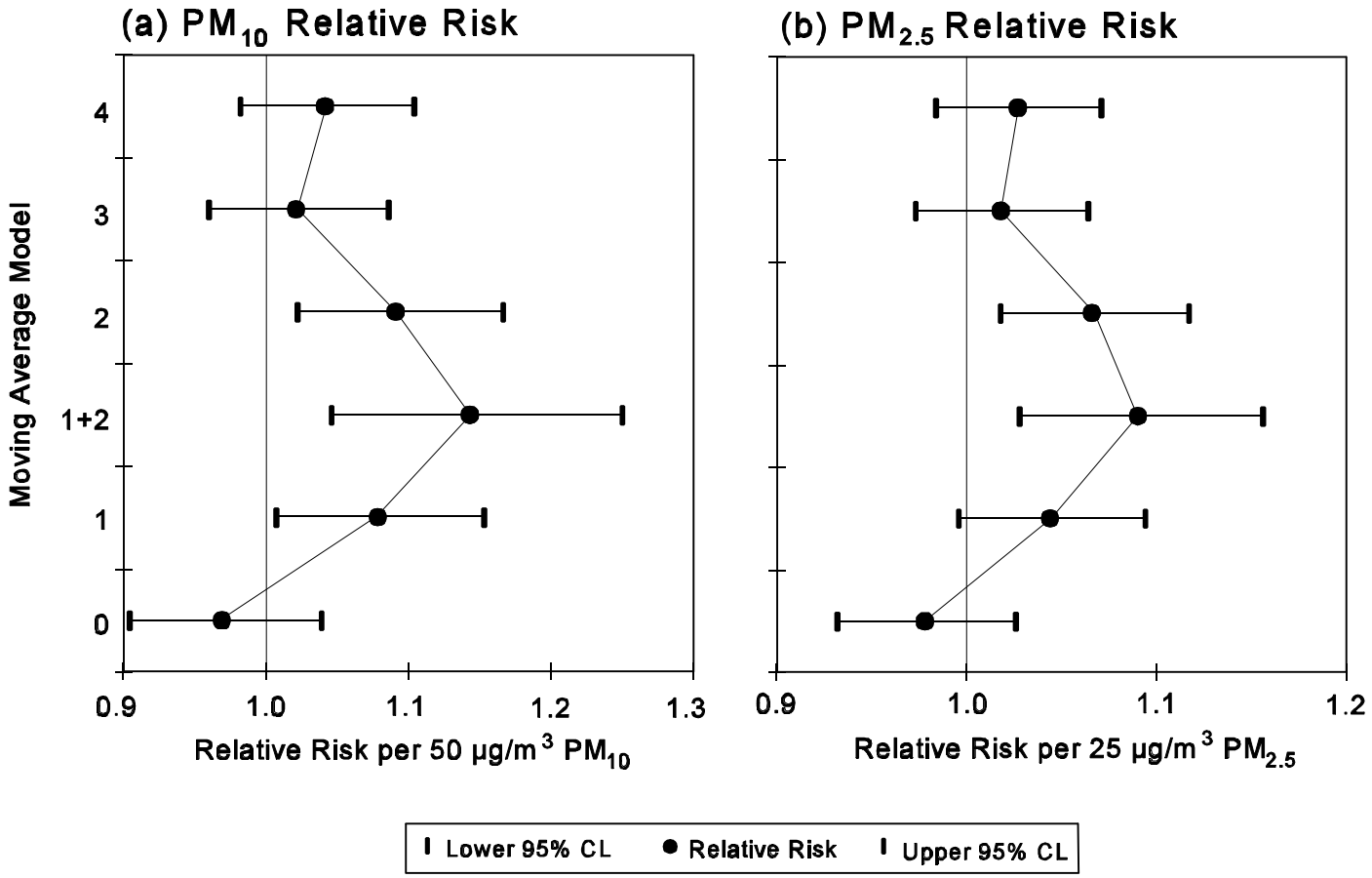

Figure 12-24. Relative risk of total mortality for particulate matter in St. Louis, as a function of moving average and lag times: (a) PM_{10} and (b)$PM_{2.5}$.

Source: U.S. EPA graphical depiction of results from Dockery et al. (1992) and Dockery (1995).

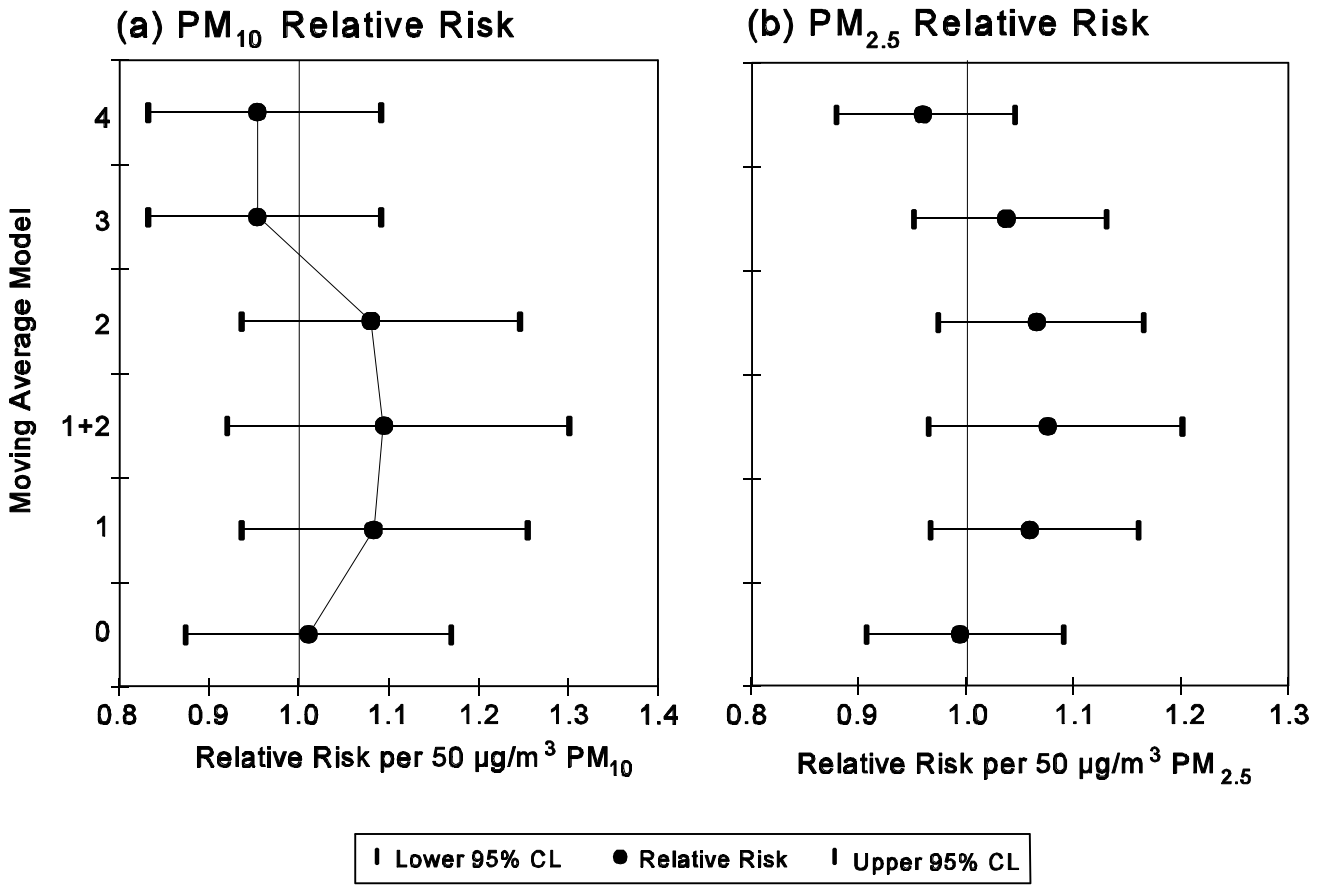

Figure 12-25. Relative risk of total mortality for particulate matter in eastern Tennessee as a function of moving average and lag times: (a) PM_{10} and (b) $PM_{2.5}$.

Source: U.S. EPA graphical depiction of results from Dockery et al. (1992) and Dockery (1995).

Longer-term moving averages were not evaluated, but the effects of PM_{10} would probably have been much smaller than the RR calculated using the average of 1- and 2-day lagged PM. As in the Utah Valley and Santiago studies, PM lag structure needed to be identified in order to obtain a significant PM effect.

Model Specification for the New York City Respiratory Mortality Study (Thurston and Kinney, 1995)

Thurston and Kinney (1995) compared several Gaussian OLS time series models with a Poisson regression model, using respiratory mortality data for New York City for 1972 to 1975. Time series were done using both unfiltered mortality and pollution data, and filtered mortality and pollution time series using a 19-day moving average. Analyses were done using year-round unfiltered OLS, April-September OLS, April-September filtered OLS, April-September adjustments by sines and cosines, and April-September Poisson regression adjusted with sines and cosines. During the April-September ozone season, the unfiltered OLS model showed a strong significant COH effect, but the COH effect size decreased to small and nonsignificant values when the filtered or detrended analyses were performed. The ozone effect size decreased somewhat from the unfiltered OLS analysis, but was similar in magnitude and statistically significant using filtered or detrended OLS, or Poisson regression models.

Model Specification for the Los Angeles Mortality Studies (Kinney et al., 1995; Ito et al., 1995)

Kinney et al. (1995) have discussed a number of important model specification issues for an air pollution time series model. Figure 12-26a,b, taken from their paper, shows the RR estimates for 100 ug/m^3 PM_{10}, with alternative methods to control for temporal cycles. In general, most such adjustments for seasonal cycles using dummy variables or Fourier series (sines and cosines) reduced the RR slightly. Subsetting the data into winter and summer groups increased the uncertainty, but did not greatly affect the RR estimate. However, the summer-only RR adjusted with 4 sine/cosine terms was larger than the unadjusted annual RR, and statistically significant. Figure 12-26b shows the results of including co-pollutants, O_3 and CO. Including O_3 in the model, along with PM_{10}, did not

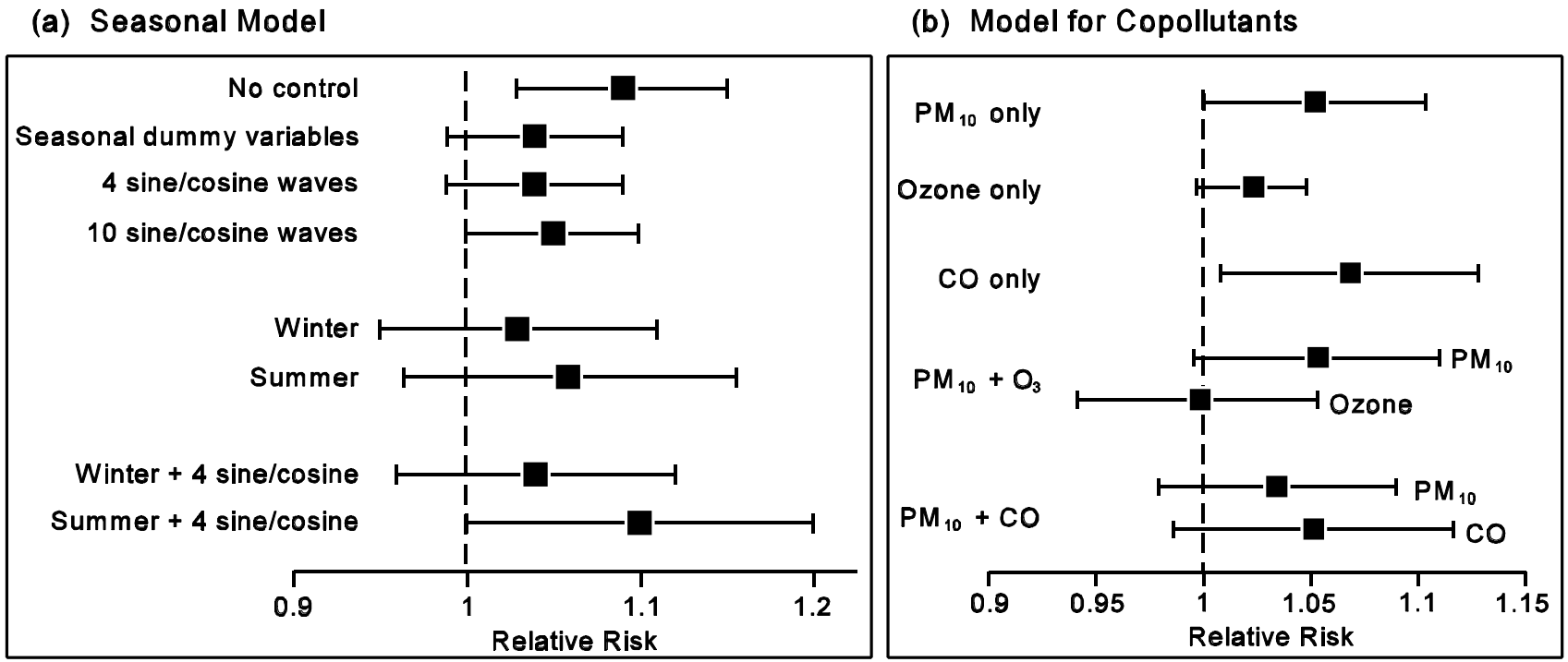

Figure 12-26. Relative risk of total mortality for PM_{10} in Los Angeles, as a function of (a) seasonal model and (b) models including co-pollutants.

Source: Adapted from Kinney et al. (1995).

change the RR for PM, but increased its uncertainty slightly so that the RR for PM became only marginally significant (two-tailed test, $p < 0.05$). Including CO in the model reduced the RR for PM, which was also less significant. CO and O_3 were too highly correlated to use in a three-pollutant model.

Ito et al. (1995) have evaluated alternative model specifications for combining data from a network of urban monitoring stations, when one station collects data daily and others at an irregular schedule, such as once-every-6-days with different days at different stations. While an important subject, this is not the primary source of concern about possible model mis-specification. The optimal use of monitoring data distributed over space and time is more likely to appear as a problem in exposure measurement error arising when any surrogate is used instead of the actual individual exposure.

Model Specification for the Chicago Mortality Studies (Ito et al., 1995; Styer et al., 1995)

Styer et. al. evaluated several alternative models for the Chicago PM_{10} study discussed in Section 12.3.1, including models that assess the effects of dividing data by season. Figure 12-27 shows the RR for total elderly mortality per 50 $\mu g/m^3$ of PM_{10} in ten different models. Model 0 is their basic best-fitting model using all of the data and assuming a common PM effect for all seasons. The next eight models deal with pairs of model specifications for PM in each season. Models 1, 4, 6, 8 are based on a single model using all of the data with dummy variables for each season that allows separate PM effects in fall, spring, winter, and summer respectively. Models 2, 5, 7, and 9 are similar models fitted independently using subsets of the data for each season. Model 3 is also a separate model for elderly mortality in fall, similar to Model 2 except that the moving average for PM is 5 days, whereas all of the other models used 3-day moving averages. In general, the RR for each season did not show large differences when different estimation methods were used, but there were large differences among seasons in these analyses. The only statistically significant RR were for fall and spring. The PM RR for winter and summer seasons did not differ significantly from 1.0.

Ito et al. (1995) also evaluated alternative model specifications for combining data from a network of urban monitoring stations in Chicago. Relative risks for models with daily

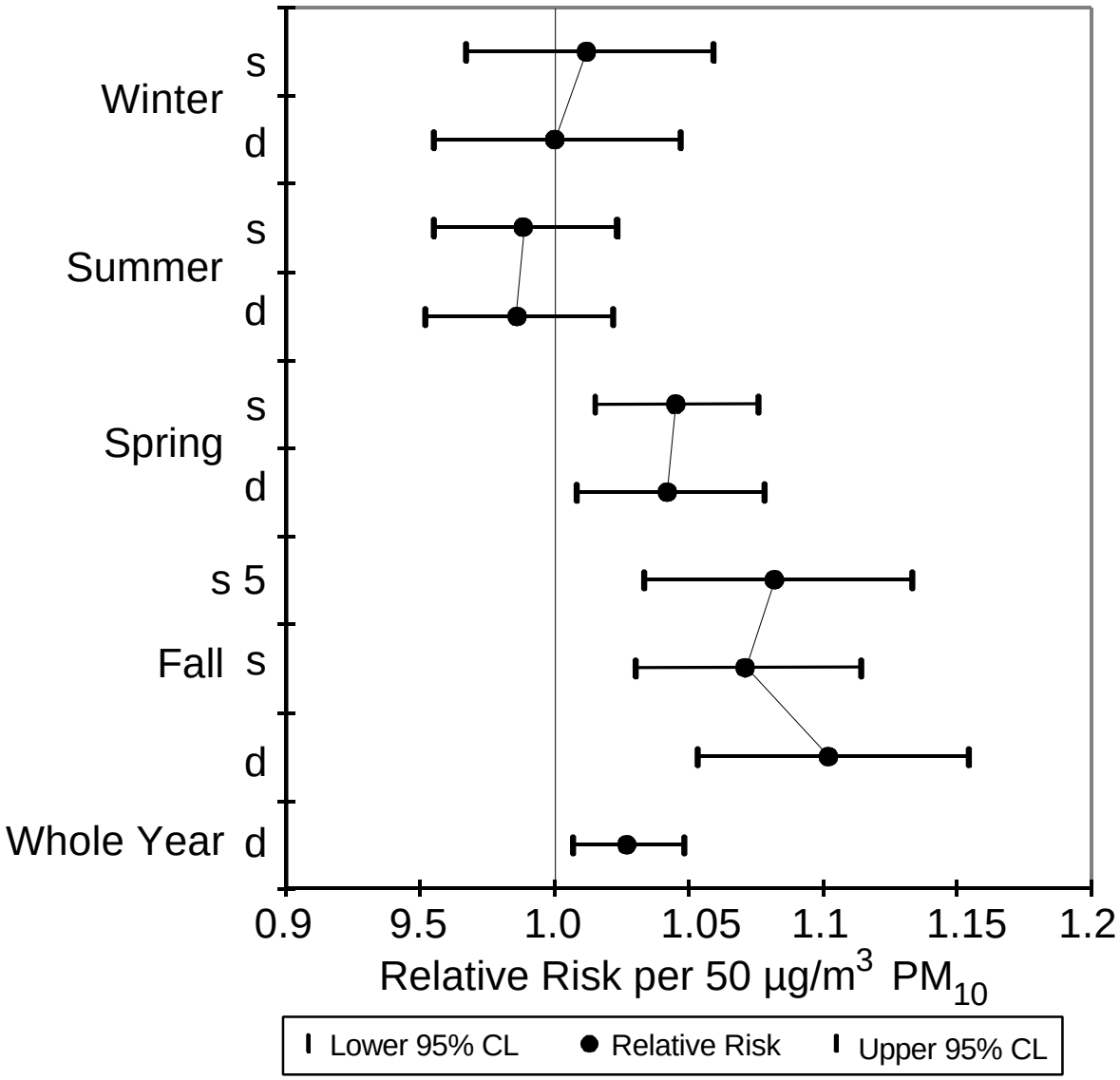

Figure 12-27. Relative risk of total mortality for PM_{10} in Chicago as a function of the model for seasons. Abbreviations: d, all of the data; s, subset of the data; S5, for models of 3 to 5 day moving average, whereas all other models used 3-day moving average.

Source: U.S. EPA graphical depiction of results from Styer et al., 1995.

PM_{10} were statistically significant using any of several alternative averaging models, such as averaging from all non-missing sites or averaging from all sites using regression-imputed PM_{10} for missing sites. Data from some individual sites also gave significant PM effects, but models using every-6-day data were generally not significant, typically because the estimated RR had greater uncertainty when only 1/6 as many data were available.

Model Specification for the Steubenville Mortality Studies (Schwartz and Dockery, 1992b; Moolgavkar et al. 1995a)

Two papers have assessed alternative treatments of a single data base, air pollution and mortality data from Steubenville, OH for 1974-1984 and, more recently, for 1981-1988 (Moolgavkar et al. 1995a). The initial analyses by Schwartz and Dockery (1992b) evaluated several Poisson regression model specifications, including a basic model with mean temperature and dewpoint (same day and lagged one day), and seasonal indicators. Neither same-day nor lagged temperature and dewpoint were statistically significant, nor the square of these variables, nor indicators for hot days (> 70 °F). However, humidity measured by mean dewpoint temperature was nearly statistically significant at the $p \leq 0.05$ level, and an indicator for days that were both hot (> 70 °) and humid (dewpoint > 65 °) was a statistically significant predictor of mortality. Sensitivity analyses included putting both average of same-day and previous day TSP and SO_2 in the model, omitting weather and season variables, including year of the study as either a random effect or as a fixed effect (no year was significant) and including an autocorrelation structure. As expected, including SO_2 reduced the TSP effect, but the decrease was small; RR for TSP decreased from 1.04 without including SO_2 to 1.03 per 100 ug/m^3 when SO_2 was included, and the SO_2 coefficient was not significant whereas the TSP coefficient was still statistically significant. As shown in Figure 12-28a, these had little effect on the estimated relative risk for 100 ug/m^3 TSP. This paper also demonstrated the use of TSP quartiles for displaying a relationship between the PM indicator and adjusted mortality or morbidity. However, TSP was used as a continuous covariate in the models because the grouping of continuous measurements into groups or categories must involve a loss of information, whether large or small.

Moolgavkar et al. (1995a) evaluated a number of Poisson regression models, with particular emphasis on seasonal subsets of the data. The whole-year models analogous to those of Schwartz and Dockery (1992b) are also shown in Figure 12-28a. The results are close to those of Schwartz and Dockery, but are not identical. The RR for 100 ug/m^3 TSP are somewhat smaller, but the decrease is only from about 1.032 to 1.025 when SO_2 is included in the model. These coefficients are for what Moolgavkar et al. define as the "restricted" mortality data set, which consists of deaths in Steubenville of people who resided

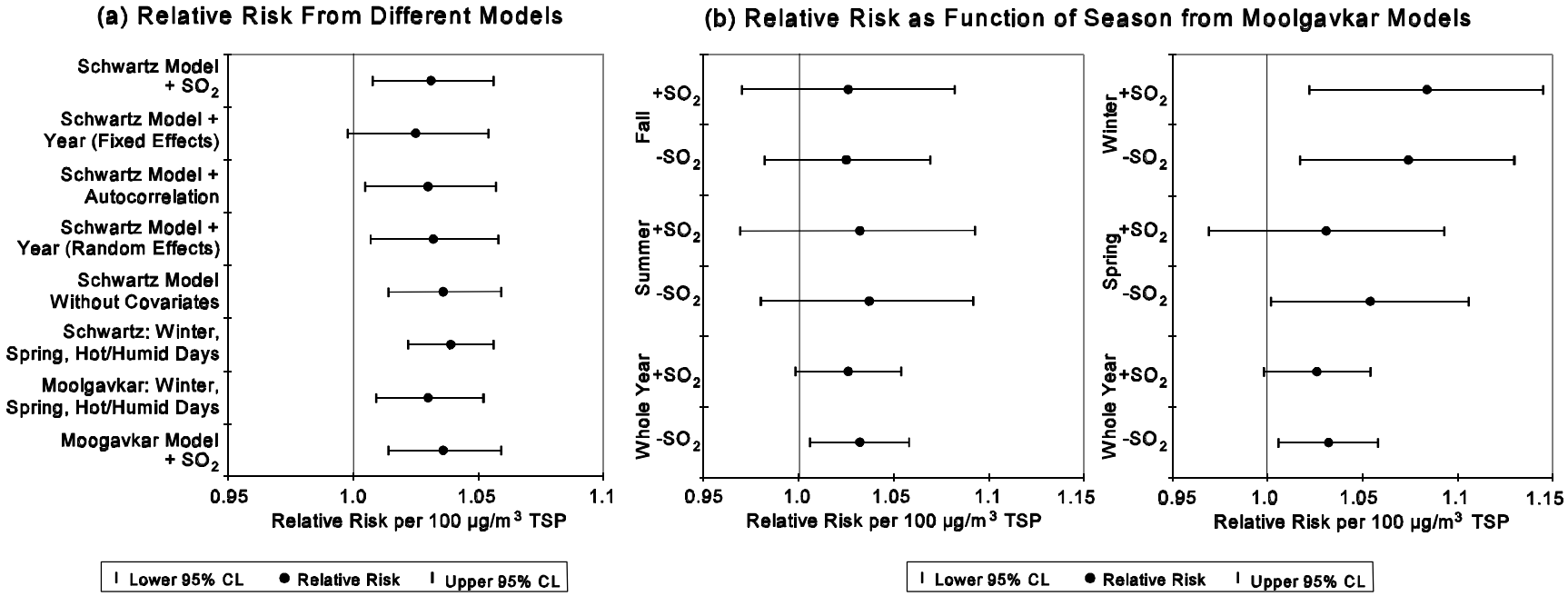

Figure 12-28. Relative risk of total mortality for total suspended particle (TSP) in Steubenville: (a) different models (left) and (b) as a function of season (center, right).

Sources: U.S. EPA graphical depiction of results from Schwartz and Dockery (1992b) and Moolgavkar et al. (1995a).

there. This is comparable to the data set used by Schwartz and Dockery in this study, and by Schwartz or Dockery and their associates in many other studies. The argument for use of the "restricted" mortality data is that community-based air monitors provide better exposure indicators for people who live in the community most of the time, as opposed to commuters or to other visitors who die in the community. Also, since many metropolitan areas contain medical facilities that may be better equipped than those in more remote areas, it is possible that some excess number of the deaths in elderly or ill patients transported from the more remote areas occur in urban centers such as Steubenville. Moolgavkar et al. (1995a) also show results for analyses of "full" mortality data, which includes individuals who did not reside in the location at which they died.

It is clear that season-to-season effects are present in these data. Schwartz and Dockery found that winter and spring mortality was significantly higher than summer and fall mortality. Moolgavkar separated the analyses by season. He found that whole-year RR for TSP was nearly the same as RR in the separate summer and fall models, with or without SO_2 in the model, and nearly the same in the spring model when SO_2 was included. However, TSP coefficients were higher in the winter, and in the spring model when SO_2 was not included. In fact, as shown in Figure 12-28b, the RR for TSP increased slightly in the winter model when SO_2 was included.

There is a possibility that the weather models used by Schwartz and Dockery, and by Moolgavkar et al. are not adequate to remove all of the seasonal effects. It is possible that additional variance reduction could have been achieved with the use of additional weather data, emphasizing more extreme conditions than the very moderate cutpoints of temperature and dewpoint, since temperature extremes are known to have effects on mortality (Kalkstein, 1991; Kalkstein et al., 1995; Kunst et al., 1993). Variables used by other investigators, such as barometric pressure, could have been tested. The flexibility of the model to fit nonlinear relationships could be improved by the use of nonparametric or semi-parametric models, and classifying data by synoptic weather category may provide a useful alternative approach to evaluating the interaction between season and weather.

Moolgavkar found that the TSP coefficients were not statistically significant (two-tailed tests at 0.05 level) in any season except winter, nor in the whole-year model, when SO_2 was included in the model. However, the season-by-season TSP coefficients were not tested in a whole-year model. Part of the non-significance may be attributable to the fact that confidence

intervals for a regression parameter in a separate seasonal model, with about 1/4 of the data in a whole-year model, may be on the order of twice (= reciprocal square root of 1/4) as wide as the confidence interval for the corresponding season-by-pollutant regression coefficient in a whole-year model, everything else being equal.

The method of adjusting the mortality series for weather effects and for other time-related effects (detrending) may be important in explaining why the RR estimates for TSP vary seasonally and why those derived by Moolgavkar et al. are quantitatively different from those derived by Schwartz and Dockery (1992b), even though the differences are small in these studies. There may exist some residual confounding with weather, since other studies have found that substantial adjustment of weather by use of temperature and dewpoint categories, or nonparametric smoothers of temperature, humidity, and time can effectively eliminate seasonal variations in residuals and in PM effect. Even so, the estimated TSP effect on RR of mortality is positive in most seasons, even in Steubenville models including the collinear co-pollutant SO_2. No adjustments were made for other pollutants such as CO, NO_x, and O_3.

These analyses of the Steubenville data set are primarily useful for demonstrating the results of different data analysis strategies and methods, since the PM indicator was TSP, not PM_{10}. These analyses have shown the desirability of adequately adjusting the analysis of pollution effects for weather and for long-term and medium-term time trends and variations. When co-pollutants were evaluated, it was evident that only part of the TSP effect could be attributed to SO_2. Differences in RR of TSP between analyses presented in the two papers are not regarded as large.

Model Specification for Philadelphia Mortality Studies (Schwartz and Dockery, 1992a; Li and Roth, 1995; Moolgavkar et al. 1995b; Wyzga and Lipfert, 1995b; Cifuentes and Lave, 1996)

Several papers have recently appeared that allow assessment of alternative treatments of a single data base, the air pollution and mortality data from Philadelphia for the years 1973 to 1980, and more recently 1981 to 1988 (Moolgavkar et al. 1995b). The initial analyses by Schwartz and Dockery (1992a) evaluated several Poisson regression model specifications, including a basic model with mean temperature and dewpoint (lagged one day), winter season temperature (same day), and an indicator for hot days (> 80 F). Sensitivity analyses included putting both average of same-day and previous day TSP and SO_2 in the model, stratifying analyses as above or below median SO_2 level (18 ppb), omitting weather and season variables, and including day of week. As

shown in Figure 12-29, these had little effect on the estimated relative risk for 100 $\mu g/m^3$ TSP. RR for mortality in the elderly was greater than for other age groups. A more detailed assessment of the age structure was presented by Schwartz (1994c), showing clearly that there was increased mortality in ages 65 to 74, and again higher at ages 75+. There was also significantly increased mortality at ages 5 to 14 years, based on a small number of cases. This paper also demonstrated the use of TSP quantiles for displaying a relationship between the PM indicator and adjusted mortality or morbidity. However, TSP was used as a continuous covariate in the models because the grouping of continuous measurements into groups or categories must involve a loss of information, whether large or small.

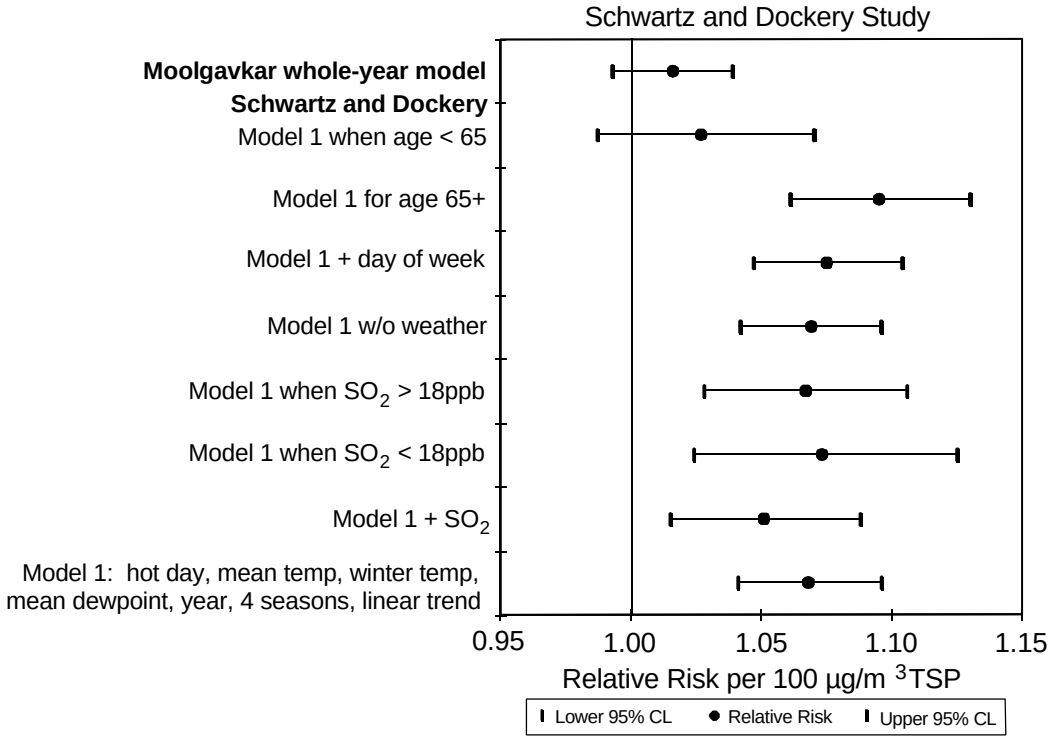

Figure 12-29. Relative risk of total mortality for total suspended particles (TSP) in Philadelphia.

Sources: U.S. EPA graphical depiction of results from Schwartz and Dockery (1992a) and Moolgavkar et al. (1995b).

Li and Roth (1995) reanalyzed these data, but only reported results in the form of t-statistics. A wide range of model specifications were tested, although some models (such as those using deviations from mean values for day of year, or from monthly average) appear to assume an unrealistic level of seasonal recurrence of air pollution and weather effects in the model most directly comparable to the Poisson regression models used by Schwartz and Dockery (1992a). The autoregressive model they denoted AR(6) was somewhat comparable to models tested in the London analyses of Schwartz and Marcus (1990). However, the models with residual deviations of mortality from 7-, 15-, or 29-day moving averages did not have comparably filtered predictors on the "right" side of the prediction equation; so the regression coefficients are not readily interpretable as predictions of mortality deviations from mean pollution levels. The Poisson log models that are most comparable to those used by other investigators involved comparisons of model specifications for averaging times. The results only indicate statistical significance by use of statistics, not effect size in any form more useful in epidemiologic studies (Greenland et al., 1986). In a model that includes TSP, SO_2, and O_3, statistical significance of TSP is clearly highest with the moving average of 0+1 day lags, and diminishes sharply for all pollutants when longer lags are included. Models with longer weather averages are also more predictive. The lower significance of the TSP term may be related to the fact that it may have greater exposure measurement error than the gaseous pollutants. The models evaluated in this paper were not adjusted for collinearity, even though there are some fairly strong collinearities in the data, such as between TSP and SO_2 and between temperature and ozone, so that inclusion of several collinear variables is almost certain to greatly inflate the variance and thus reduce the statistical significance of many of the regression coefficients.

Moolgavkar et al. (1995b) evaluated a number of Poisson regression models, with particular emphasis on seasonal subsets of the data. These are shown in Figure 12-30a-d. It is clear that season-to-season effects are present in these models. The models were adjusted for weather and time trend by using quintiles of temperature and indicators of year. There is a possibility that the weather model is not adequate to remove all of the seasonal effects. Subdividing the temperature range by quintiles will result in three or four closely spaced quintiles corresponding to moderate temperatures which have little effect on mortality, and will not adequately take into account temperature extremes. Quintiles of temperature are not

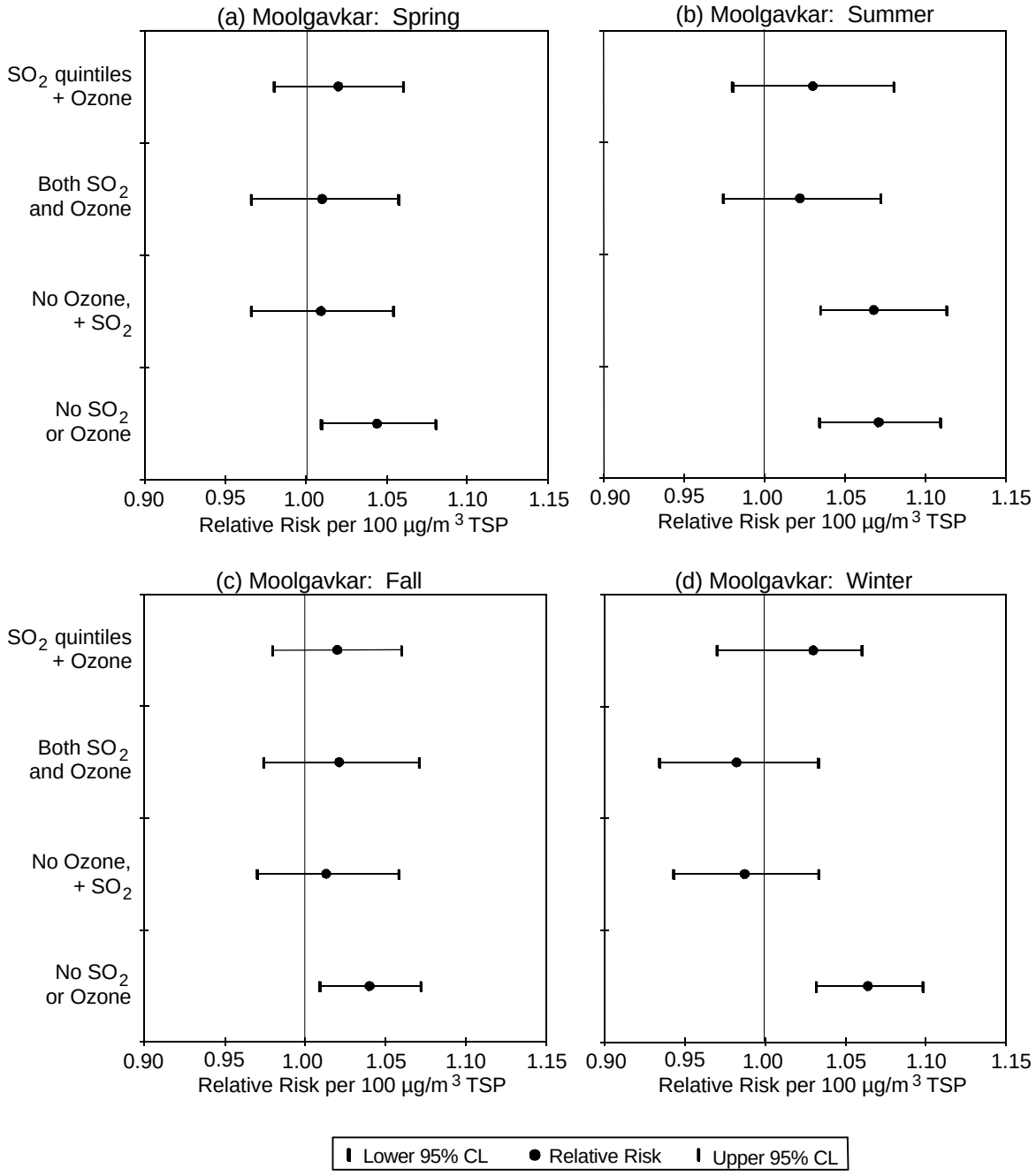

Figure 12-30. Relative risk of total mortality for total suspended particles (TSP) in Philadelphia, in the (a) spring, (b) summer, (c) fall, and (d) winter.

Source: U.S. EPA graphical depiction of results from Moolgavkar et al., 1995b.

given here, but Li and Roth (1995) report values of maximum temperature at the 10th, 25th, 50th, 75th, and 90th percentiles as 37, 48, 63, 78, and 84 degrees F; and Schwartz and Dockery (1992a) report mean temperature percentiles corresponding to 25, 36, 52, 66, and 73 degrees F, respectively. This paper finds a significant effect for the highest quintile in the summer and the lowest quintile in the other seasons, suggesting that additional variance reduction could have been gained by the use of additional weather data, emphasizing more extreme conditions than the 20th and 80th percentiles and possibly including information on dewpoint or barometric pressure (as used by other investigators). In general, replacing numeric data by grouped equivalents such as quintile classes involves some loss of information. The loss of information may be acceptable if there is a corresponding increase in the flexibility of the model to fit nonlinear relationships, but in this instance the loss of information may be substantial since extreme temperatures are known to have a quantifiable and increasing relationship with mortality as the temperatures become more extreme (Kunst et al., 1993). The method of adjusting the mortality series for weather effects and for other time-related effects (detrending) may be important in explaining why the RR estimates for TSP vary seasonally and are quantitatively different from those derived by Schwartz and Dockery (1992a). There may exist some residual confounding with weather, since other investigators have found that substantial adjustment for weather by use of temperature and dewpoint categories or by nonparametric smoothers of temperature, humidity, and time can effectively eliminate seasonal variations in residuals and in PM effect. Even so, the estimated TSP effect on RR of mortality is positive in most seasons, even in models including collinear co-pollutants SO_2 and O_3.

Neither the Schwartz and Dockery (1992a) study nor the Moolgavkar et al. (1995b) study allows a complete assessment of the actual role of co-pollutants as confounders of a PM effect. While SO_2 is not as strongly correlated with temperature as is O_3, it is also subject to weather conditions that affect atmospheric dispersion along with TSP. Therefore, if there is an incorrect assignment of weather effects on mortality, some part of the mortality that could have been explained with weather-related variables will probably be allocated to various other predictors of mortality used in the models, especially TSP and the co-pollutants. The development of a predictive model for mortality using weather and other time-varying covariates would probably have required use of humidity, since humidity along with temperature had been predictive of mortality in earlier studies, such as for London (Schwartz and Marcus, 1990) and Steubenville

(Schwartz and Dockery, 1992b). If confounding can be explained by an unobserved (or in this case, unused) covariate, then omission of humidity from any of the models in the Moolgavkar et al. (1995b) study is certainly another candidate explanation for the differences in results between these papers. However, both papers may also have provided an inadequate adjustment for other medium-term effects on a scale longer than a day and shorter than a season or quarter, such as for epidemics. The use of nonparametric smoothers such as LOESS, or GAM models of time, would allow subtraction of such trends. Even a simple alternative, such as including a dummy variable for every month in every year (96 parameters for the 1973-1980 series; another 96 parameters for the 1981-1988 series) would probably have greatly improved the ability of these analyses to evaluate short-term responses to short-term changes in air pollution and weather. The parameters that relate mortality to pollution and weather over intervals of a few days were likely the same or similar over periods of some years and would require only a few more parameters. In view of these questions, we regard potential confounding among TSP, SO_2, and summer ozone in Philadelphia that was identified in the Moolgavkar et al. (1995b) study as possible, but not yet proven.

Another unresolved issue is that TSP may have relatively larger exposure measurement error than the gaseous pollutants. Since TSP includes large particles, TSP levels are more associated with local sources and transport near the air pollution monitors and show a weaker correlation with TSP at other monitors than is the case for smaller particles. In particular, TSP would be expected to show less correlation within the Philadelphia area than would PM_{10}, and even less yet than would $PM_{2.5}$ across the area. Therefore, TSP may be less predictive of individual PM exposure than the smaller size PM indicators in Philadelphia. Since variables with larger exposure measurement error are more likely to show attenuated effects (bias towards smaller RR) than covariates with smaller measurement errors, it is at least possible that SO_2 may spuriously appear to be a more important predictor of pollution-related mortality than does TSP. There does not seem to be any way to evaluate these possibilities from the published reports.

Wyzga and Lipfert (1995b) also reanalyzed the Philadelphia time series data for 1973 to 1990, using Gaussian OLS regression models with time-lagged predictors. In view of the moderately large number of deaths per day (21 deaths at ages less than 65 years, 34.5 deaths at ages 65 and older), the OLS regression coefficients are probably sufficiently accurate approximations to regression coefficients estimated from Poisson regression models. They

evaluated model specifications for daily mortality, log mortality, and deviations of mortality from 15-day moving averages. The regression models were adjusted for maximum temperature dummy variables in 6 categories, winter season, daily changes in barometric pressure, and time trend. Maximum hourly O_3 was evaluated as a co-pollutant. The RR estimates for TSP were calculated using regression coefficients and standard errors in their Table 3, plus data from their Figures 14 and 20. Figure 12-31a shows RR for ages <65 years, Figure 12-31b for ages 65+ years, for all days (N = 2380) and for N=390 hot days (maximum temperature at least 85 degrees), for different averaging times. The largest and most significant estimates of TSP effect, measured as deviations from 15-day moving averages, are in the elderly, especially on hot days. For the elderly on hot days, the TSP effect is nearly the same for averaging times from 2 to 5 days on hot days, but the 0+1 day moving average has only slightly greater statistical significance than thee 0+1+2+3 and 0+1+2+3+4 day averages. When all days are considered, the RR for TSP is only half as large and statistically significant only for 0+1 day TSP averages. For deaths at age <65, none of the all-day TSP RR values were significant; on hot days, the 0+1 average TSP was nearly significant, and the 0+1+2 day average TSP effect nearly as large, but other RR estimates were much smaller. The estimates were not calculated using filtered pollution series, but the moving averages of TSP had some of the same effect of removing long-term trends and effects. These estimates are in general similar to those found by Schwartz and Dockery, but larger differences were found for other model specifications. This paper did not attempt to include SO_2 as a covariate, since TSP was clearly collinear with SO_2.

These analyses of the Philadelphia data set are primarily useful for demonstrating the results of different data analysis strategies and methods, since the PM indicator was TSP, not PM_{10}. These analyses have shown the desirability of adequately adjusting the analysis of pollution effects for weather and for long-term and medium-term time trends and variations. When co-pollutants were evaluated, it was evident that only part of the TSP effect could be attributed to O_3, and that the O_3 effect was more nearly confounded with temperature and season than with TSP. However, there was a substantial degree of confounding between

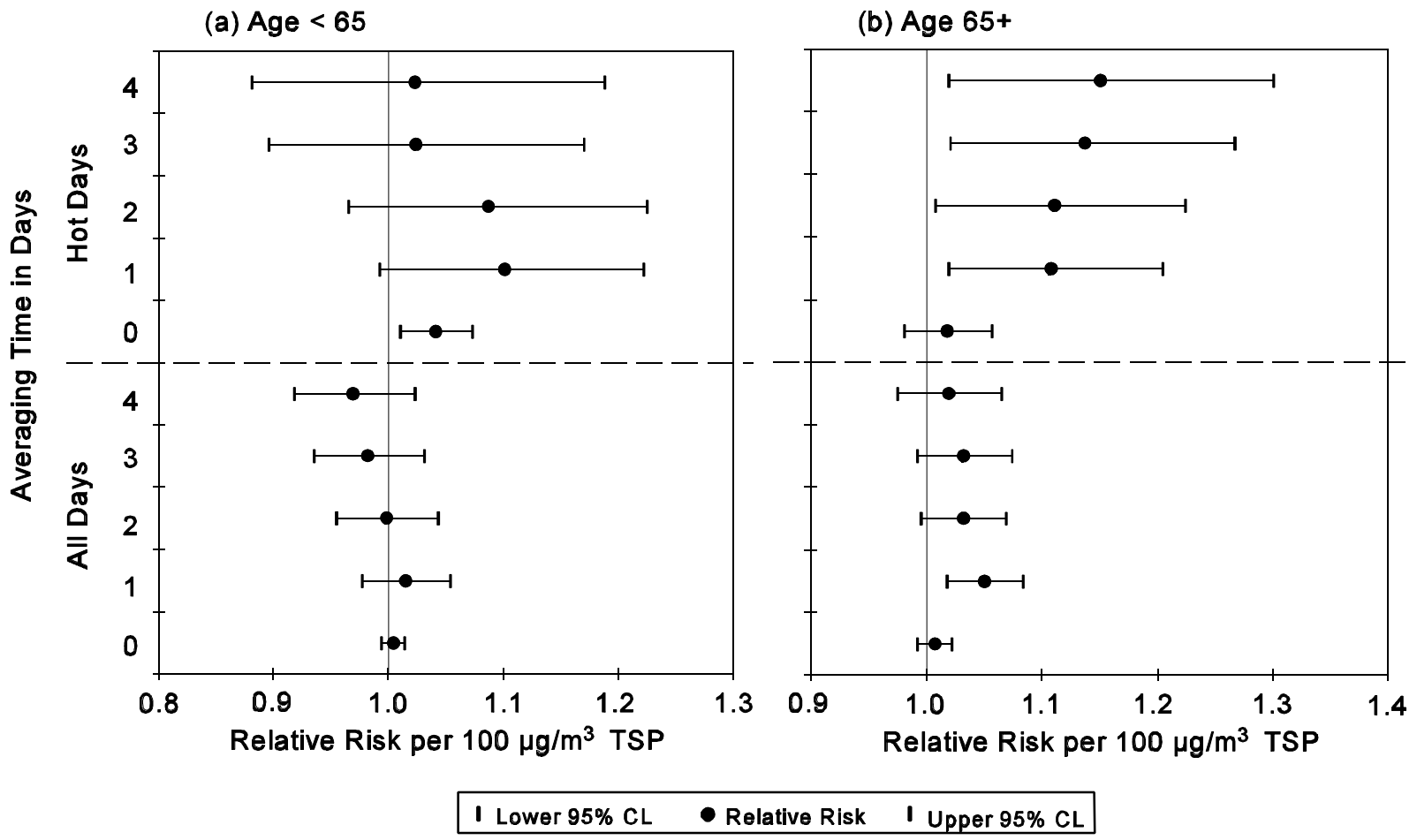

Figure 12-31. Relative risk of mortality for TSP in Philadelphia, as a function of age, averaging time, and temperature: (a) age < 65; (b) age > 65.

Source: U.S. EPA graphical depiction of results from Wyzga and Lipfert (1995b).

TSP and SO_2 effects, which could be separated in some analyses but not in all analyses. The best averaging time for pollution was 0+1 days, but longer averages seemed useful in estimating RR among the elderly during hot weather.

Models with Additive Linear Specification for Multiple Pollutants

The relationship between Philadelphia mortality and some potentially confounding pollutants has recently been reexamined by Samet et al. (1996a). The results from tables 7,8, and 11 of their report are summarized in Table 12-26. They fitted models for total mortality, cardiovascular mortality, respiratory mortality, and mortality for other non-external causes, for the period 1974 to 1988. Models were fitted for whole-year data using adjustments for weather, season, time trends, and for five pollutants: TSP, SO_2, O_3, NO_2, and CO. The results shown here in Table 12-26 are for whole-year total mortality averages of current-day and previous-day pollutant concentrations, and a lagged CO variable denoted LCO that includes the 2-day average CO from 3 and 4 days earlier, as predictors of total mortality in a Poisson regression model with seasonal adjustments. They report results from their models somewhat differently than in this document, as the percent increase in mortality per increase over the inter-quartile range (IQR) of the pollutant. While we have established standard increments for TSP and SO_2, we have not defined standard increments for the effects of the other pollutants and so we report their results in the same form as in their report. The most important findings from Samet et al. (1996a) are: (a) CO never has a significant concurrent effect; (b) LCO has a stable significant effect; (c) O_3 has a stable significant effect; (d) the TSP coefficient is reduced if SO_2 is in the model increased when NO_2 is in the model; (e) the SO_2 coefficient is reduced when TSP is in the model and increased when NO_2 is in the model; and (f) the NO_2 coefficient is small and not significant unless TSP or SO_2 are in the model.

Table 12-26 shows the IQR effects for 17 models reported by Samet et al. (1996a). Model 1 shows the regression coefficients using all six pollutant averages. The superscript “1" shows that the coefficients would be regarded as statistically significant, with the t statistic (ratio of coefficient estimate to asymptotic standard error estimate) between 2 and 4, except for TSP with t = 1.962, and CO which is not at all statistically significant. Models 2 and 3 show results with omission of LCO and omission of CO respectively. To compare

TABLE 12-26. EXCESS RISK ESTIMATES FOR SIX AIR POLLUTION INDICES, FOR PHILIDELPHIA, 1973-1988. COEFFICIENTS ARE PERCENT EXCESS TOTAL MORTALITY PER INTERQUARTILE RANGE IN POLLUTANT CONCENTRATION.

Model	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17
POLLUTANTS	TSP	TSP	TSP	TSP	TSP	---	TSP	TSP	TSP	TSP	---	---	---	---	---	---	---
	SO_2	SO_2	SO_2	SO_2	---	SO_2	---	---	---	---	SO_2	SO_2	SO_2	SO_2	---	---	---
	O_3	O_3	O_3	---	---	---	O_3	---	---	---	O_3	---	---	---	O_3	O_3	O_3
	NO_2	NO_2	NO_2	---	---	---	---	NO_2	---	---	---	NO_2	---	---	---	NO_2	---
	CO	CO	---	---	---	---	---	---	CO	---	---	---	CO	---	---	---	CO
	LCO	---	LCO	---	---	---	---	---	---	LCO	---	---	---	LCO	LCO	---	---
TSP	1.04[1]	0.95	1.06[1]	0.74	1.15[1]	---	0.96[1]	1.79[2]	1.43[1]	1.21[1]	---	---	---	---	---	---	---
SO_2	1.08[1]	1.08[1]	1.08[1]	0.60	---	1.08[1]	---	---	---	---	1.05[1]	1.45[1]	1.23[1]	1.12[1]	---	---	---
O_3	1.95[1]	2.15	1.91[1]	---	---	---	2.04[1]	---	---	---	2.25[1]	---	---	---	2.11[1]	2.27[1]	2.37[1]
NO_2	-1.14[1]	-1.15[1]	-1.10[1]	---	---	---	---	-0.93[1]	---	---	---	-0.63	---	---	---	0.14	---
CO	0.08	0.09	---	---	---	---	---	---	-0.54	---	---	---	-0.38	---	---	---	0.27
LCO	1.07[1]	---	1.10[1]	---	---	---	---	---	---	1.17[2]	---	---	---	1.16[2]	1.04[1]	---	---
AIC[3]	---	74.9	66.5	---	81.7	82.0	74.4	---	------	---	72.5	---	---	---	71.4	78.8	78.7

[1] $2 \leq |t| < 4$, except for Model 1, which has t = 1.04/0.53 = 1.962 from Table 11.
[2] $|t| \geq 4$
[3] AIC - 16,400, from Table 8, where the Akaike Information Criteria (AIC) assesses goodness of fit.

Source: Samet et al. (1996a).

competing mortality prediction models, Samet et al. (1996a) used Akaike's Information Criterion (AIC) (15, 16). This index of model fit combines the deviance, which measures the fidelity of the model predictions to the observed data, with a penalty for adding more predictor variables. In the comparison of two models A and B, the model with lower AIC is preferred. If the AIC for model A is 5(10) units smaller than that for model b, this means that a new observed mortality series would be 10(150) times more likely to have occurred under model a than model b. Model 4 shows that fitting total mortality only with TSP and SO_2 results in greatly reduced and non-significant coefficients, although the TSP coefficient is reduced less than is the SO_2 coefficient. Model 5 shows that fitting the mortality time series with only TSP produces a goodness of fit that is somewhat inferior to the goodness of fit of Models 2 and 3 with 5 pollutants, where the AIC for Model 5 is 16,481.7 compared to AIC = 16,474.9 for Model 2 and AIC = 16,466.5 for Model 3. Relatively small differences in AIC should not be overinterpreted. Model 6 with only SO_2 produces a slightly worse fit than Model 5. Model 7, with TSP and O_3, produces a sightly better fit than Model 2 after adjusting for the fact that Model 2 includes three additional pollutants: SO_2, NO_2, and CO. However, Model 11 with SO_2 and O_3 produces a somewhat better fit than Model 7 with TSP and O_3, and Model 15 with O_3 and LCO a better fit than Model 11. The other models in Table 12-26 show all pairwise combinations of pollutants including either TSP, SO_2, or O_3.

Samet et al. (1996a) conclude that "... a single pollutant of the group TSP, SO_2, NO_2, and CO cannot be readily identified as the best predictor of mortality, because concentrations of the four pollutants were moderately correlated in Philadelphia during the years of this study ... We advise caution in interpreting model coefficients for individual pollutants in models including such correlated pollutants. Insights into the effects of individual criteria pollutants can be best gained by assessing effects across locations having different pollutant mixtures and not from the results of regression models of data from single locations."

Some of the issues related to confounding from co-pollutants are discussed in Sections 12.6.3.4 and 12.6.3.5, and the usefulness of assessments from multiple sites with different pollutant mixtures is noted there. However, further study of the analyses in Samet et al. (1996a) suggests that at least some of these issues may be capable of resolution by more complete analyses of the Philadelphia data. Our purpose in evaluating the potential for confounding among co-pollutants is to determine whether different pollutants are so closely related in every season as to preclude any possibility of separating their effects on health. While confounding is not the

same as collinearity in general, there is little reason to believe that pollutant concentrations adjusted for weather and season have non-monotonic or strongly nonlinear relationships, so that we may use collinearity diagnostics as convenient characterizations for potential confounding in this case. Season-specific differences among potentially confounded pollutants may also be present. The pollutant indices used in the Poisson regression models are averages of same-day and previous-day concentrations, whereas the correlation matrices in Samet et al. (1996a) are for each single day.

EPA has evaluated the potential for copollutant confounding using the correlation matrices reported in Table 6 of Samet et al. (1996a). The authors reported partial correlation coefficients of TSP, SO_2, O_3, NO_2, and CO adjusted for weather and time trends, for the whole year and by season. EPA carried out principal components analyses of these correlation matrices (shown in Table 12-27). The principal values of a correlation matrix are all non-negative and add up to the number of variables in the matrix, so that the average principal value = 1. Many textbooks and papers (Belsley et al., 1980) suggest that for ordinary least squares regression analyses, collinearity is unlikely to be a problem if the condition number of the correlation matrix (ratio of largest to smallest principal value) is less than about 30, or roughly speaking, if the smallest principal value is greater than about 0.05. The smallest principal value for any copollutant correlation matrix is 0.228 and the largest condition number for any season is 14.5 for winter, as shown in Table 12-28. In other words, at worst, copollutants can only moderately confound the TSP effect.

Detailed assessment of principal components of the seasonal correlation matrices in Table 12-29 shows some important similarities. First of all, O_3 is virtually absent from the main factor (explaining 52 to 58% of the variance of the five pollutants) for spring and autumn, and O_3 is the virtually unique second factor explaining 22 to 24% of the variance. Thus, O_3 does not confound any of the TSP or other copollutant findings for these seasons. During summer and winter, O_3 is a somewhat larger component of the overall pollutant factor (which only accounts for 50% of the variance), but CO is a somewhat smaller component, whereas the second principal component for summer is primarily the difference between O_3 and CO. The third principal component is primarily the difference between SO_2

TABLE 12-27. CORRELATION MATRICES FOR FIVE POLLUTANTS IN PHILADELPHA FOR THE YEARS 1974-1988, ADJUSTED FOR TIME TRENDS AND WEATHER, FOR EACH SEASON

	TSP	SO_2	O_3	NO_2	CO
Spring					
TSP	1.000	0.584	0.198	0.624	0.388
SO_2	0.584	1.000	0.031	0.578	0.344
O_3	0.198	0.031	1.000	-0.065	-0.294
NO_2	0.624	0.578	-0.065	1.000	0.664
CO	0.388	0.344	-0.294	0.664	1.000
Summer					
TSP	1.000	0.552	0.368	0.572	0.308
SO_2	0.552	1.000	0.293	0.551	0.214
O_3	0.368	0.293	1.000	0.279	0.026
NO_2	0.572	0.551	0.279	1.000	0.482
CO	0.308	0.214	0.026	0.482	1.000
Fall					
TSP	1.000	0.697	0.134	0.757	0.564
SO_2	0.697	1.000	0.035	0.660	0.442
O_3	0.134	0.035	1.000	0.041	-0.241
NO_2	0.757	0.660	0.041	1.000	0.657
CO	0.564	0.442	-0.241	0.657	1.000
Winter					
TSP	1.000	0.716	-0.367	0.700	0.574
SO_2	0.716	1.000	-0.470	0.683	0.535
O_3	-0.367	-0.470	1.000	-0.516	-0.462
NO_2	0.700	0.683	-0.516	1.000	0.727
CO	0.574	0.535	-0.462	0.727	1.000

Source: Samet et al., 1996a.

TABLE 12-28. PRINCIPAL VALUES OF THE PRINCIPAL COMPONENTS OF TSP AND ITS COPOLLUTANTS IN PHILADELPHIA FOR THE YEARS 1974-1988, BASED ON CORRELATION MATRICES IN TABLE 12-27

Season	Component Number					Condition Number
	1	2	3	4	5	
Spring	2.606	1.233	0.558	0.353	0.250	10.42
Summer	2.537	1.016	0.660	0.427	0.359	7.07
Fall	2.899	1.129	0.491	0.253	0.228	12.71
Winter	3.326	0.679	0.501	0.265	0.229	14.52

Source: U.S. EPA calculations based on results reported by Samet et al. (1996a).

and CO except in summer, where it is the difference between SO_2 and O_3 plus CO. The fourth principal component is primarily the difference between TSP and SO_2 and accounts for 5 to 8% of the variance, which may explain in part why separating these pollutants in the absence of other information may be difficult. The fifth principal component, accounting for 5 to 7% of the pollutant variance, includes NO_2 as the major component, but with differences between NO_2 and TSP in autumn, between NO_2 and CO in spring. Additional analyses without ozone in the pollutant mixture are shown in Table 12-30. The principal values are not shown because they are quite similar to those in Table 12-27 except for the absence of component 2, representing ozone, and a corresponding increase in the principal value for component 3. The principal components of the four-pollutant mixture in Table 12-30 are quite similar from season to season. There is a primary component 1 in which all four pollutants are given similar weight, representing 65 to 72% of the non-ozone variance. This corresponds to overall high or low levels in all four pollutants, and is likely to be inversely related to wind speed. Component 2 largely reflects the differences between SO_2 (representing stationary sources) and CO (representing mobile sources) in all seasons, explaining 15 to 20% of the variance, with TSP making a relatively minor contribution to the SO_2 component loading. Component 3 largely represents the difference between TSP and SO_2 in all seasons, and explains 7 to 10% of the non-ozone pollutant variance in each season. Component 4 consists primarily of NO_2 in spring, summer, and winter; it appears to contrast NO_2 with TSP in the fall, and it explains 6 to 9% of the variance. Thus, it seems

TABLE 12-29. PRINCIPAL COMPONENTS OF THE POLLUTANTS FOR PHILADELPHIA IN THE YEARS 1974-1988, BASED ON THE CORRELATION MATRICES IN TABLE 12-27

Season		Component Loadings				
Spring	Pollutant	1	2	3	4	5
	TSP	0.803	0.363	0.006	-0.462	0.102
	SO_2	0.773	0.203	-0.534	0.255	0.102
	O_3	-0.058	0.923	0.315	0.209	0.039
	NO_2	0.899	-0.067	0.155	0.075	-0.396
	CO	0.742	-0.451	0.387	0.159	0.266
Summer						
	TSP	0.822	0.112	0.117	-0.542	0.072
	SO_2	0.771	0.146	0.472	0.315	0.251
	O_3	0.506	0.676	-0.519	0.123	0.043
	NO_2	0.845	-0.197	0.020	0.126	-0.481
	CO	0.546	-0.698	-0.391	0.062	0.242
Fall						
	TSP	0.894	0.184	-0.032	-0.292	0.284
	SO_2	0.824	0.122	-0.490	0.259	-0.006
	O_3	-0.000	0.963	0.235	0.128	0.005
	NO_2	0.909	0.037	0.113	-0.155	-0.367
	CO	0.772	-0.387	0.427	0.246	0.109
Winter						
	TSP	0.836	0.361	-0.171	-0.358	0.113
	SO_2	0.843	0.175	-0.365	0.345	0.075
	O_3	-0.664	0.717	0.183	0.099	0.037
	NO_2	0.901	0.054	0.156	0.002	-0.401
	CO	0.814	-0.027	0.530	0.088	0.219

Source: U.S. EPA calculations based on results reported by Samet et al., 1996a.

that TSP effects can be substantially distinguished from those of NO_2 (except possibly in the autumn) and can be reasonably distinguished from those of CO in all seasons. O_3 may be a potential confounder in summer, but not otherwise. The most consistent potential confounder

TABLE 12-30. PRINCIPAL COMPONENTS OF FOUR POLLUTANTS FOR PHILADELPHIA IN THE YEARS 1974-1988, BASED ON THE CORRELATION MATRICES IN TABLE 12-27, EXCLUDING OZONE

Season		Component Loadings			
Spring	Pollutant	1	2	3	4
	TSP	0.810	-0.331	0.464	0.139
	SO_2	0.776	-0.444	-0.439	0.091
	NO_2	0.899	0.167	0.018	-0.405
	CO	0.734	0.629	-0.070	0.246
Summer					
	TSP	0.810	0.245	-0.521	0.112
	SO_2	0.771	0.435	0.396	0.254
	NO_2	0.864	-0.084	0.102	-0.486
	CO	0.608	-0.758	0.048	0.230
Fall					
	TSP	0.894	0.160	0.301	0.291
	SO_2	0.824	0.443	-0.355	-0.011
	NO_2	0.909	-0.054	0.195	-0.364
	CO	0.772	-0.595	-0.200	0.103
Winter					
	TSP	0.869	0.279	0.402	0.072
	SO_2	0.852	0.377	-0.344	0.119
	NO_2	0.906	-0.149	-0.043	-0.391
	CO	0.818	-0.523	-0.021	0.237

Source: Samet et al., 1996a.

for TSP is SO_2, but even here, the collinearity is not so severe as to discourage further analyses. It would therefore seem possible that a structured approach to evaluating copollutant interrelationships would allow construction of more realistic TSP exposure indices than simply using the mean of TSP, SO_2, NO_2, and CO. A conceptual basis for modelling discussed in Section 12.6.3.5 illustrates what these data suggest, i.e., that NO_2 and SO_2 are primary pollutants and that TSP is partly a secondary pollutant - including components generated from SO_2 and NO_2. The analyses by Samet et al. (1996a) represent a first step in this direction.

A more direct assessment of potential confounders is based on simply evaluating the stability of the TSP effect or other pollutant effects when other pollutants are included in the model. This is, in many contexts, among the least biased of all confounder selection methods (Mickey and Greenland, 1989). A review of Table 12-26 shows that the TSP effect changes by more than 10% from a base value of 1.06 (Model 3) when O_3 is *not* included as a covariate, and when SO_2, NO_2, CO, or LCO are included (Models 4, 8, 9, 10). The TSP effect is: reduced by 30% when SO_2 is included; reduced by 10% when O_3 is included; increased by 14% when LCO is included; increased by 35% when CO is included (although the CO effect is *negative*); and increased by 70% when NO_2 is included (although the NO_2 effect is significantly *negative*, more likely indicative of collinearity than a beneficial health effect from NO_2 exposure). The SO_2 effect is more sensitive to the inclusion of TSP, a 44% reduction, than is the TSP effect to inclusion of SO_2. There is also a smaller increase of the SO_2 effect when NO_2 or CO are included. The O_3 and LCO effects are nearly invariant, suggesting that they may be important covariates, but not confounders of TSP or SO_2 effects. We cannot assess the effects of models that include O_3, LCO, and some combination of two or more pollutants including TSP. In particular, the effects of O_3 and LCO on the simultaneous estimates of TSP and SO_2 would be of interest.

Cifuentes and Lave (1996) also evaluated additive linear models using combinations of TSP, SO_2, and O_3, but with results for the years 1983 to 1988 that differ somewhat from those derived by Moolgavkar et al. (1995b). The results are summarized in Table 12-31 for each season and for the whole year, showing all combinations in which at least one pollutant was used to fit the total mortality time series. The time series were adjusted for weather and for time trends. The most consistently predictive pollutant in these models is TSP. Model 1, with all three pollutants, shows a significant TSP effect for spring and for autumn, with smaller effects that are not quite statististically significant at the 0.05 level for summer and winter. SO_2 effects are positive only in winter, but not significant. Model 2 shows similar results without including O_3, with a somewhat larger and statistically significant effect for TSP in summer. When TSP is the only pollutant used as a predictor of mortality in Model 3, it is similar in magnitude and statistically significant in all seasons. When SO_2 is used

TABLE 12-31. RELATIVE RISKS OF TOTAL NON-EXTERNAL MORTALITY FOR ADDITIVE LINEAR MODELS USING TSP, SO_2, AND O_3 IN PHILADELPHIA, 1983 TO 1988. INCREMENTS ARE 100 $\mu g/m^3$ FOR TSP, 100 $\mu g/m^3$ FOR SO_2, 100 ppb FOR O_3

		Model						
Season		1	2	3	4	5	6	7
		TSP	TSP	TSP	---	TSP	---	---
		SO_2	SO_2	---	SO_2	---	SO_2	---
		O_3	---	---	---	0_3	O_3	O_3
Spring	TSP	1.087[1]	1.090[1]	1.080[1]	---	1.078[1]	---	---
	SO_2	0.956	0.960	---	1.036	---	1.012	---
	O_3	1.010	---	---	---	1.005	1.039	1.041
Summer	TSP	1.079	1.088[1]	1.081[1]	---	1.074[1]	---	---
	SO_2	0.979	0.984	---	1.067	---	1.027	---
	O_3	1.013	---	---	---	1.010	1.037	1.040[1]
Autumn	TSP	1.090[1]	1.114[1]	1.093[1]	---	1.076[1]	---	---
	SO_2	0.986	0.977	---	1.050	---	1.044	---
	O_3	1.150[1]	---	---	---	1.130[1]	1.184[1]	1.160[1]
Winter	TSP	1.056	1.050	1.081[1]	---	1.095[1]	---	---
	SO_2	1.050	1.039	---	1.064[1]	---	1.079[1]	---
	O_3	1.108	---	---	---	1.094	1.115	1.081
All Year	TSP	1.076[1]	1.088[1]	1.093[1]	---	1.082[1]	---	---
	SO_2	1.011	1.008	---	1.058[1]	---	1.052[1]	---
	O_3	1.032[1]	---	---	---	1.031[1]	1.045[1]	1.050[1]

[1]95% Confidence Interval > 1.

Source: Cifuentes and Lave (1996) Tables 6 and 7.

alone in Model 4, it is statistically significant only in winter. The TSP effect is nearly the same in Model 5 when O_3 is also used as a covariate, suggesting little confounding between O_3 and TSP.

Concentration-Response Models with Piecewise Linear Components

Cifuentes and Lave (1996) have evaluated several important classes of alternatives to the log-linear Poisson models fitted by other investigators, using Philadelphia TSP data for 1983-1988 in which both daily SO_2 and ozone data were also available. Their results are shown in two forms in the paper: (1) restriction to subsets of data below a given level of TSP; (2) piecewise linear models with specified values of the joint point c. The results for the latter are shown in their Table 10 and Figure 4. These models fit in the more general form:

$s(PM) = a\ PM$ if $PM < c$,

$s(PM) = b\ (PM - c) + d$ if $PM > c$.

A continuous piecewise linear function or linear spline has $d = ac$, and a discontinuous function has $d \neq ac$. The subset and piecewise continuous functions for c = 59 $\mu g/m^3$ (the 50th percentile of TSP) and for c = 91 $\mu g/m^3$ (the 90th percentile of TSP) are shown in Figure 12-32. For the subset of analyses using same-day TSP values the apparent statistical significance of the estimated RR shows a slight decrease with decreasing sample size as the cutoff concentration c (not necessarily a concentration at which the two linear segments intersect) decreases to 100 $\mu g/m^3$.

The results for continuous piecewise linear models are shown in Figure 4 of Cifuentes and Lave (1996). The upper half of the the piecewise linear relationship is consistently high (RR of 1.04 to 1.08 for all cut points c = 30 to 90 $\mu g/m^3$), and is statistically significant except for the small number of data points above 90 $\mu g/m^3$. The lower half of the piecewise linear model also shows a strong relationship to TSP (RR of 1.047 to 1.055) for TSP at cut points of 90 $\mu g/m^3$ or above, with general statistical significance. There is little relationship in the lower part of the piecewise linear fit for cutpoints between 30 and 60 $\mu g/m^3$. This suggests that there are some substantial deviations from a purely linear additive models involving TSP and certain covariates or copollutants at TSP levels below 100 $\mu g/m^3$, but that the deviations are not necessarily indicative of a “threshold” model with slope 0

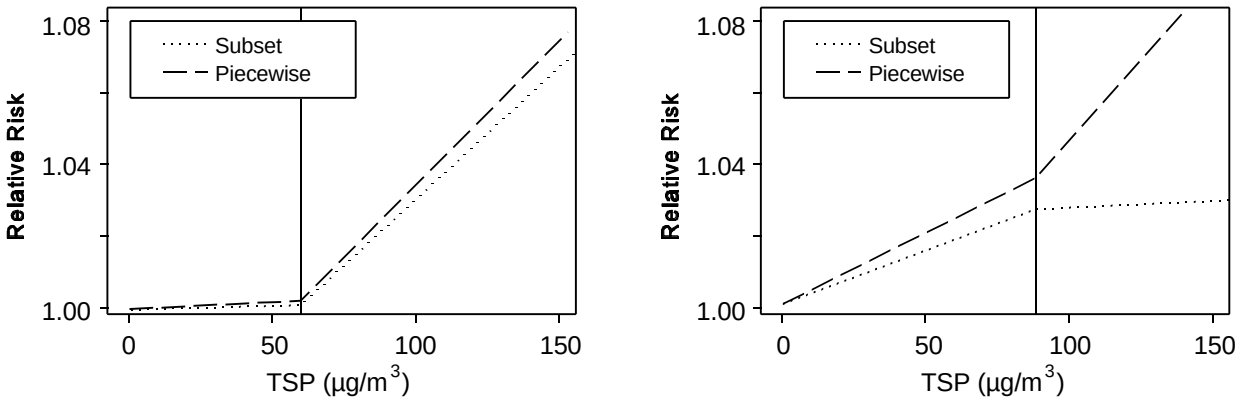

Figure 12-32. Relative risk of death versus total suspended particles (TSP) level for each of the models used to explore the threshold levels, for disease deaths. The model includes SO_2 and O_3, as well as control for weather using the full specification. The breakpoints are at 59 $\mu g/m^3$, the 50th percentile of TSP, and at 91 $\mu g/m^3$, the 90th percentile of TSP.

Source: Cifuentes and Lave (1996).

(RR = 1.00) below some cutoff level c as shown in Figure 12-32. While Cifuentes and Lave show the results of fitting a nonparametric loess smooth model of temperature and dewpoint, there is no analogous nonparametric model for TSP shown in the paper.

The HEI study (Samet et al., 1995) largely confirmed the additive linear model estimates derived by other investigators, and so will not be shown here. A major new finding from this study is that the marginal mortality-pollution curves for TSP and the two-dimensional smooth response surfaces fitted to mortality data using both of these pollutants was significantly nonlinear and nonadditive. This is discussed below in evaluating copollutant models.

Model Specification Using Fine Versus Coarse Versus Thoracic Particle Indices

The recent reanalyses of the Six City Study by Schwartz et al. (1996) allow evalution of the effects of thoracic particles (PM_{15}), fine particles (FP = $PM_{2.5}$), or coarse particles (CP = PM_{15} - $PM_{2.5}$) as exposure indices. The reported results were transformed to standard increments of 50 $\mu g/m^3$ PM_{15}, 25 $\mu g/m^3$ $PM_{2.5}$, and 25 $\mu g/m^3$ for CP, as shown in Figure 12-33.

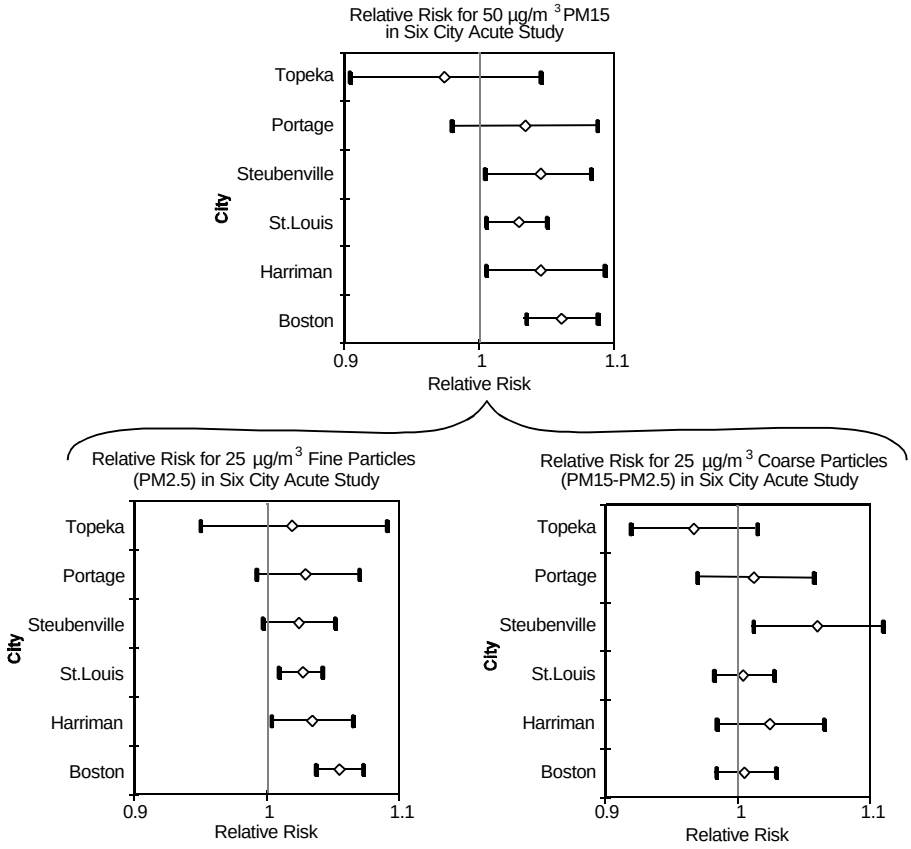

Figure 12-33. Relative risks of acute mortality in the Six City Study, for inhalable particles (PM_{10}, PM_{15}), fine particles ($PM_{2.5}$) and coarse particles (PM_{15}-$PM_{2.5}$).

Source: U.S. EPA graphical depiction of results from Schwartz et al. (1996).

It is clear that, across the six cities, $PM_{2.5}$ is the most predictive of the three PM indices except in Steubenville, where a more significant CP effect was found (although the FP effect size for Steubenville was nearly as large as in most other cities). In spite of very considerable differences among the cities in terms of climate and demographics, the FP effect sizes were rather consistent. The CP effect sizes were positive, small, and not significant except for Steubenville (positive, significant) and Topeka (negative, nearly significant). Since PM_{15} was the sum of FP and CP, it had an intermediate significance, with positive and significant effects except for Portage and Topeka. The St. Louis and Harriman/Knoxville associations for PM_{15} and FP were both significant, possibly because of the use of nonparametric smoothers to adjust for weather and time trends. Overall, the pattern of results obtained most strongly implicates fine particles ($PM_{2.5}$) as

contributing to PM-mortality relationships in the subject six cities. The Steubenville results suggest that, in some cases, CP may also need to be considered as well as FP in evaluating PM health risks.

Model Specification for Other Mortality Studies

Other studies on acute mortality have evaluated alternative model specifications. A number of OLS and time series regression models for COH in Santa Clara were compared by Fairley (1990). Mortality studies for Detroit (Schwartz 1991a) and Birmingham (Schwartz, 1993a) evaluated other regression and time series approaches. These are not reported in as much detail as the studies cited here, and the Detroit study also uses estimates for PM. Lipfert and Wyzga (1995a,b) also compare many of the above mortality studies using elasticity as a risk index.

12.6.2.2 Model Specification for Morbidity Studies

There have been a large number of recent studies on hospital admissions related to PM (Schwartz, 1993b, 1994b, 1994e, 1995a, 1995b, 1996). These have used generally similar strategies for evaluating alternative Poisson regression models. The basic model includes a set of variables for temperature and dewpoint (usually in 6 to 8 categories), linear and quadratic time trends, indicators or dummies for each month in each year (so that no assumptions need to be made about recurrent seasonal or monthly effects), and the PM indicator. Alternative model specifications usually include: (1) piecewise cubic spline functions for time trend, temperature, and dewpoint; (2) generalized additive models (GAM) for time trend, temperature, and dewpoint; (3) basic model, excluding all non-attainment days (PM_{10} > 150 ug/m^3, or ozone > 120 ppb, etc.); (4) basic model without hot days; (5) extended range of lag times or moving averages; (6) basic model plus co-pollutants. Differences in RR for PM among most specifications is small. RR estimates from the GAM method tend to be higher than most other specifications, but the conclusions about RR are fairly insensitive to alternative specifications. Since there have been no studies that disagree with these conclusions, these are not reviewed below in detail, since the assessments are in many ways similar to those for the acute mortality studies.

12.6.2.3 Model Specification Issues: Conclusions

Published research articles have provided a substantial amount of evidence about the consequences of different model specifications for short-term and long-term models. The short-term studies have been generally consistent across many different kinds of model specifications. The general concordance of PM effects, particularly in analyses of short-term mortality studies, is a consequence of certain appropriate choices in modelling strategy that most authors have adopted, but the results are not dictated by the use or misuse of any specific model. While it is conceivable that different plausible model specifications could lead to markedly different conclusions, this has not emerged thus far.

12.6.3 Other Methodological Issues for Epidemiology Studies

The issues in air pollution epidemiology for PM are similar to those of many other pollutants. No single air pollutant, nor any mixture such as PM or an identifiable component of PM, is uniquely related to a specific health outcome. Also, in the PM studies individual exposure measurements are generally lacking, with exposure to PM typically measured at only one site in an urban or regional airshed or, at most, at a few widely spaced sites. U.S. studies of acute mortality typically depend on combining three data bases: (1) mortality data tapes provided by the National Center for Health Statistics (NCHS); (2) air pollution data sets for urban areas, accessed through the Aerometric Information Retrieval System (AIRS) network; and (3) meteorological data for urban areas and smaller SMSA's, obtained from the National Climatic Data Center (NCDC). Hospital admissions data involve a more diverse set of sources. Merging the data sets has not always been a straight-forward task, and attempts to replicate results have sometimes been complicated by the fact that different investigators have used different approaches to creating a merged data set for subsequent analyses. As a simple example, the PM_{10} monitoring data for Chicago consists of every-day monitoring at one site and every-6-days monitoring at up to eight other sites. In that case, different investigators may calculate different PM_{10} concentrations according to how the data from the intermittent monitoring sites are combined with data from the every-day site. In this section, specific methodology issues encountered in the studies reviewed earlier are discussed.

12.6.3.1 Particulate Matter Exposure Characterization

PM_{10} measures the inhalable particles better than TSP. The U.S. EPA NAAQS are specified by PM_{10} concentrations, which were not generally available before 1986. PM_{10} is also a better index of ambient fine particle exposure than TSP because it is more uniformly distributed in an urban area or region than TSP. Since fine particles from outside can also penetrate indoors and constitute a major fraction of indoor air concentrations, PM_{10} is also likely to be a better index of indoor air exposure to ambient fine particles than TSP. Currently, PM data on AIRS do not allow discrimination among important components of PM_{10}, including fine particles, coarse particles, or sulfates. In the absence of any clearly demonstrated mechanistic relationship between PM components (by size, composition, or source) and specific health endpoints, there is little a-priori reason to believe that health endpoints related to PM should not be predicted well in different studies by different PM indices. The indices include PM_{10}, fine particles (defined as $PM_{2.5}$), coarse fraction of PM_{10} particles (defined as PM_{10} - $PM_{2.5}$), or surrogates (e.g., sulfates, SO_2, or H^+) that may be more closely correlated with fine particles than to coarse particles. Results presented by Dockery and Pope (1994b) suggest that $PM_{2.5}$ may be a more appropriate "proxy" of exposure to particles that are predictive of health effects. This has also been generally supported by Schwartz et al. (1996), although there appears fully to be some situations, such as in Steubenville, where coarse particles cannot be ruled out as contributing to observed PM-health effects relationships.

$PM_{2.5}$ particles are more likely to be uniformly distributed within an urban airshed and, upon penetrating indoors, to be removed less rapidly from indoor air than coarse particles, so that outdoor ambient fine particle concentration becomes a better predictor of total fine particle exposure than ambient coarse particle concentration does for total coarse particle exposure. However, it is not clear that inhalable coarse particle fractions (i.e., PM_{10}-$PM_{2.5}$) can be entirely discounted in terms of their potential health effects. While sulfates are a significant part of fine particle levels in some places, they may be of more limited value as an indicator of a toxic component of PM_{10} due to measurement artifacts (filter artifacts). The usefulness of sulfate data may also be limited because of regional and seasonal differences of sulfate levels. Information on other components of PM_{10}, including acidity, metal ions, and organic components, is often not available. Similarly, data deficiencies exist for most co-pollutants. In studies where SO_2 is a good proxy for PM_{10}, it may be difficult to assign effects to one or the other without evaluating the relationships linking the two, since SO_2 is the source of some fraction of particle sulfates.

Chapter 7 on Human Exposure to PM indicates that variations in ambient PM concentration can be significantly correlated, on a longitudinal (day-to-day) basis, with the variation of individual personal PM exposures as measured by personal monitors. However, cross-sectional correlations of individual exposures with ambient PM concentrations are typically low. In terms of community air pollution, a properly sited ambient PM measurement is reasonably related to the mean personal PM exposure of the community, and on a time series basis it may be a good indicator of the variability of any single individuals' daily PM exposure. An important consideration here is that the ambient monitors be properly sited in relation to the populations they are intended to represent. This would have to be evaluated study by study, which can be difficult or impossible if pertinent data were not been reported for the study. There must be limits to the acceptability to using a monitor for daily level changes in regards to both the distance from the population and the terrain between the population and the monitoring site (e.g., a mountain range).

Data are available at more than one monitoring site in a few studies, including Birmingham AL (Schwartz, 1993a, 1994e), Utah Valley (Pope et al., 1992, 1994), Los Angeles (Kinney et al., 1995; Kinney and Ozkaynak, 1991), San Francisco Bay area (Fairley, 1994), Philadelphia (Wilson and Suh, 1995), and Chicago (Ito et al., 1993, 1995; Styer et al., 1995). While PM_{10} varies from place to place, with a decreasing correlation with increasing distance across a metropolitan area, measurements are well correlated up to a few kilometers (Burton et al., 1996). Fine particle measures (e.g., $PM_{2.5}$ and sulfate) are particularly well correlated across a metropolitan region.

Exposure Relevance

The majority of the PM data used in the PM/mortality literature are daily observations, rather than the standard every-6th-day observations. The ambient daily mean PM levels reported in these PM/mortality studies of U.S. cities range from 28 $\mu g/m^3$ (St. Louis, MO) to 58 $\mu g/m^3$ (Los Angeles, CA) for PM_{10}; 76 $\mu g/m^3$ (Cincinnati, OH) to 111 $\mu g/m^3$ (Steubenville, OH) for TSP. Other PM indices in the literature include CoH (monthly mean range = 9 to 12) in Santa Clara County, CA; and KM (mean = 25) in Los Angeles County, CA. The data description reported for these PM indices indicate a generally skewed distribution, and the maximum daily values deviate about 50 to 150 $\mu g/m^3$ from these means. The current 24-h NAAQS, 150 $\mu g/m^3$, is rarely exceeded in these communities. Many of these communities studied were urban, but the

PM levels observed appeared to be representative of metropolitan areas where substantial fractions of the U.S. population reside.

Size and Chemistries

In theory, since TSP includes particle sizes ($d_a < 50\ \mu m$) that exceed those having thoracic deposition ($d_a < 10\ \mu m$), it is expected that TSP would be a less reliable measure of particulate matter for health effects analyses. However, comparison of the significance of the PM regression coefficients in the recent U.S. PM/mortality studies do not show systematically lower significance for TSP than PM_{10}. This may be because, so long as TSP levels fluctuate together with smaller particles over time, TSP may still be a reasonable surrogate for thoracic or fine particles, albeit not as good as PM_{10}. The error introduced by large particles depends on their local availability and, therefore, it is site-specific.

In most of the PM/mortality time series studies, only one PM index was employed. An exception is the study conducted in St. Louis, Mo. and Kingston, TN (Dockery et al., 1992). In this study, PM_{10}, $PM_{2.5}$, sulfates, and aerosol acidity were available. The regression results indicate that, for both cities, PM_{10} showed the most significant mortality associations, and the significance declined as the size of the index decreased. However, the sample size of this study was relatively small (n = 300; PM_{10} coefficient t-ratio = 2.17 in St. Louis, and 1.07 in Kingston), and the sample size for the aerosol acidity was even smaller (n = 200). Furthermore, we currently do not know the extent to which the measurement errors of these different PM measures affect PM/mortality significance. Thus, it is as yet premature to relate the significance of various PM measures to size or chemistry specific causality from this study. Cross-sectional studies reported more significant mortality associations for fine particles ($PM_{2.5}$: Dockery et al., 1993; sulfates: Ozkaynak and Thurston, 1987). However, significant PM/mortality associations have also been reported in areas where summertime sulfates are not the major component of PM (e.g., winter analysis of Santa Clara, CA; Los Angeles, CA). All the PM measures in the U.S. studies do include some type of combustion source originated particles (e.g., automobile emissions in Los Angeles, sulfates in the eastern U.S.). Overall, PM composition varies widely, not only between sites, but also over time at a single site. This represents a major challenge to any attempts to quantify PM-related health impacts.

12.6.3.2 Exposure-Response Functions, Including Thresholds

A PM threshold for mortality is difficult to detect because of small numbers of deaths (especially when broken down by age group and cause of death), and because the observed PM concentration is only a surrogate for exposure. In general, the threshold question has not been extensively examined except by Cifuentes and Lave (1996). Even in their analyses, there is no precise estimate of a change point in the relationship, with values of TSP in the range of 60 to 90 $\mu g/m^3$ as possible cutpoints. Other model specification issues that have had little examination include non-linear transformations of pollutant variables, interactions among pollutant variables, and interactions between meteorological variables and pollutants.

Thresholds

Many of the recent U.S. PM/mortality studies have reported PM/mortality "exposure-response" curves of the data, after controlling for weather and seasonal variables (Schwartz, 1993a, 1994a; Schwartz and Dockery, 1992a; Pope et al., 1992). Measurement error is a limiting factor in the ability to detect thresholds, no matter what methods are used. Some of the smoothed curves are shown in Figure 12-34. Some estimates were constructed by using quintile or quartile indicator variables in the regression, or by nonparametric smoothing (in the Generalized Additive Models), both of which should allow for possible non-linear relationships. In all the figures presented, a generally monotonic increase in mortality, as PM increases, is suggested. However, a search for a threshold from these results is difficult because of the distribution of the available number of datapoints. For example, in the plots of the quintile (or quartile) PM versus relative risk, the resolution of the shape of slope is determined by the number (5 or 4) of indicator categories. The lowest quintile (or quartile) could be higher than a potential threshold level (e.g., the lowest quintile of TSP was about 50 $\mu g/m^3$ in Philadelphia), or other discontinuities might be present at some higher level if finer level breakdown of the data were feasible. However, because estimation of more stable

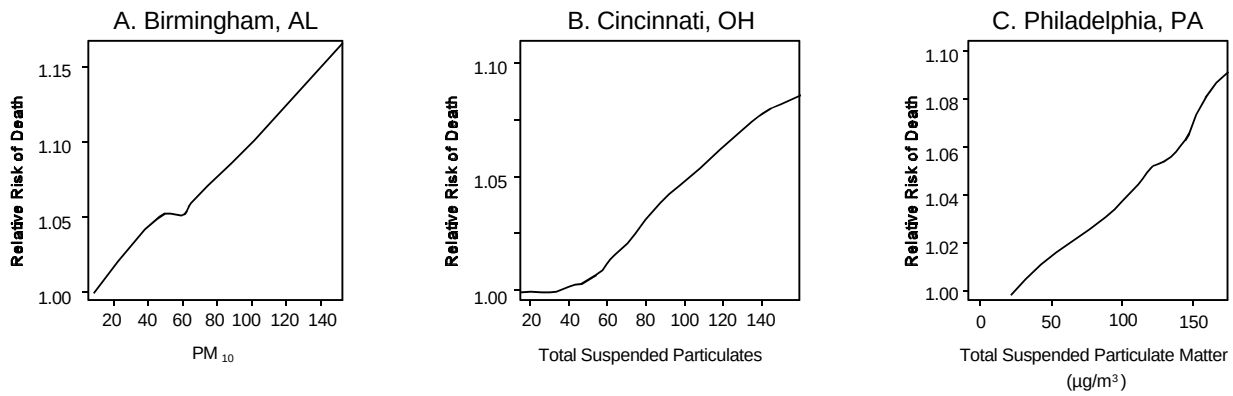

Figure 12-34. Smoothed nonparametric estimate of relative risk of mortality in three studies, where the particulate matter index is either total suspended particulates or PM_{10}, in micrograms per cubic meter.

Source: A. Schwartz (1993a), B. Schwartz (1994a), C. Schwartz and Dockery (1992a).

coefficients requires greater numbers of cases, even a large dataset may not allow smaller data division than quintiles. Thus, from these results, we cannot determine if any threshold exists below approximately 50 $\mu g/m^3$ for TSP or 20 $\mu g/m^3$ for PM_{10} or if other discontinuities exist in the range of the observed data. Samet et al. (1995) derived quintile estimates for many of the studies cited here; but the quintile estimates derived by Samet et al. (1995) were based on the observed PM values in each study, whereas those derived by Schwartz and by Pope were based on adjusted PM values on weather and time.

Nonparametric smoothing of relative risk versus PM can, in theory, allow greater resolution of the shape. However, the stability of the results also depends on the weights of neighborhood and the interval of the PM, or "span", used to compute each segment of the curve (these parameters are not described in the relevant publications). Again, these smoothed curves, as with the quintile approach, cannot describe the shape of the curve where data do not exist. For example, the smoothed curve shown in Figure 12-34 for Cincinnati, OH, appears to suggest a threshold around 40 $\mu g/m^3$ of TSP, but the distribution (25th percentile TSP = 53 $\mu g/m^3$) indicates that there are not enough data points below 40 $\mu g/m^3$ to obtain stable curve shape below this level. Lack of data densities and confidence intervals makes any detailed examination more difficult. Thus, while these figures do collectively suggest a linear-like PM/mortality relationship,

any examination of a threshold level is limited by the data. Most other studies did not consider or present graphical examination of the possible shape of any exposure/response relationship and, thus, the results could have been constrained by the functional form specified in the regression model.

Samet et al. (1995) exhibits smooth nonparametric concentration-response functions for TSP and SO_2 (Figure 11 in their report), for all ages, ages < 65, and 65+. For all ages mortality and over 65 mortality, there appears to be a piecewise linear response which increases only for TSP > 100 $\mu g/m^3$ (all ages) or TSP > 60 $\mu g/m^3$ (age 65+). The SO_2 relationship is quadratic. However, the nonparametric smooth response surface for TSP and SO_2 differs significantly from this simple threshold model.

12.6.3.3 Adjustments for Seasonality, Time Lags, and Correlation Structure

Trends, long-term and medium-term recurrent or cyclical effects, and effects of medium-term non-recurrent or random events such as influenza epidemics are removed from the data so that short-term responses to short-term changes in PM concentration can be detected without confounding or interference from longer-term effects. For Gaussian time series models, this can usually be done well by filtering. However, filtering has the potential to remove longer-term effects of PM exposure, and therefore may underestimate the true PM effect. For example, death may occur from PM exposure during the first few days after exposure because the PM exposure may exacerbate pulmonary insufficiency in individuals whose respiratory capacity has already been compromised, especially the elderly and the ill. This may also contribute to excess short-term cardiovascular mortality. However, if PM exposure also compromises the immune system, the exposed individual may succumb to an infectious disease some weeks after the PM exposure, an effect that would be more likely to be cancelled out by application of filtering or other detrending techniques. Detrending could also be done by using regressors that are functions of the time or day of study. Candidate regressors are Fourier series (sums of sine and cosine terms), polynomial functions of time, dummy variables for year, season or quarter, month, or day of week. Fourier series are mathematically convenient, but require many terms in order to fit asymmetric seasonal variations, and cannot include random year-to-year differences in seasonal effects. Dummy variables for year, season, and month provide a great deal of flexibility, but may still be too "rough" in that such models allow abrupt changes between December 31, 1980 and January 1,

1981, between June 30 and July 1, and so on. Non-parametric smoothers such as spline functions, LOESS smoothers, and generalized additive models are often good choices, but as with any other detrending procedure, the scale or span of the smooth detrender determines what medium-term effects are removed from the model.

A number of short-term studies have provided reasonable control over time-related exogenous changes. The use of tapered high-pass filters in Gaussian time series models, in connection with linear time trends or dummy variables for season or day of week, has been demonstrated in numerous papers, for example, among acute mortality studies: (Shumway et al., 1988; Schwartz and Marcus, 1990; Kinney and Ozkaynak, 1991; Ito et al., 1993; Thurston and Kinney, 1995; Kinney et al. 1995; Ito et al., 1995).

Mortality Displacement

It is possible that there is a causal effect of airborne PM, but rather than altering the long term average mortality rate, peaks in exposure simply advance the date of death of otherwise terminally ill subjects. The terms "mortality displacement" or "harvesting" have generally been applied to this hypothesis. Under this scenario, lowering particulate matter concentrations might grant a few extra days life to a small part of the population, but have no effect on the general mortality rate. It is obviously extremely important for policy making purposes to resolve whether this is indeed the case.

Although the possibility has been discussed in several of the papers reviewed (Lipfert and Wyzga, 1995a,b), only a few (Spix et al., 1993; Cifuentes and Lave, 1996) seem to have offered a serious test of the hypothesis. They point out that the effect of harvesting should be to induce a negative effect on the autocorrelation, since "a high number of deaths on one day may leave a smaller number of vulnerable individuals at risk of dying on succeeding days." They further suggest that the magnitude of this effect should be proportional to the excess deaths due to pollution. Hence, they test the hypothesis by adding an interaction between the pollutant level on that day and the last k days mortality deviation from the expected value, where the expected value is based on a previously fitted model including trend, season, and influenza epidemics. A negative estimate for this interaction term would be interpreted as evidence for this phenomenon. Applying this test to data from Erfurt, East Germany, Spix et al. found a weak effect for suspended particles in the expected direction (nominal one-tailed $p = 0.07$ ignoring the multiple

testing for k): the RR comparing the 5th and 95th percentiles of the exposure distribution was 1.51 if the previous 18 days mortality was above expected, 1.26 if it was below expected. A somewhat similar approach, examining mortality displacement from summer heat waves, has been described by Kalkstein et al. (1994).

Cifuentes and Lave (1996) examined short-term mortality displacement in two different ways. One method was to look at mortality autocorrelation coefficients. Total mortality showed a negative correlation at lag 2 days, and deaths outside of hospital inpatients had negative autocorrelation for lags 1 and 2 days. This is consistent with depletion of a potentially susceptible population by acceleration of death by 1 or 2 days, but is not a strong demonstration of the hypothesis.

A much more detailed analysis was based on the definition of "episodes" by Cifuentes and Lave. Episodes are contiguous periods of time in which pollution levels tend to be relatively elevated. They identified more than 100 such 3-day "episodes" during the 6 year period. Positive residuals (excess mortality) during the episode and negative residuals after the episode suggest displacement of mortality during that episode. However, the number of deaths occurring after the episode was typically smaller than the number occurring during the episodes suggesting that some of the excess deaths occurring during the episode were not among people who were certain to die within a few days anyway. Different methods for estimating the number of deaths, for time lags etc., produce different estimates of short term displacement. Alternative explanations such as unusual weather events cannot account for the mortality deviations observed during that period of time. Additional analyses of this reported effect would be of great interest including evaluation of out-of-hospital deaths.

The estimates comparing the first day of a three-day episode and the first day after an episode are shown in Table 12-32, for three age groups (Cifuentes and Lave, 1996; Table 10). The mean residuals are based on the best fitted model, using TSP, SO_2, and O_3. The mean number of deaths is greated than predicted on the first day of the episode. For total mortality, the excess is 0.874 deaths against 1.98 predicted for the given TSP level, or an excess of 0.874 / 1.98 = 44%. For the first day after the episode, there is a deficit of 0.895 deaths less than the 1.68 expected at the smaller post-episode value of TSP, or a

TABLE 12-32. MEAN OF TSP, MODEL RESIDUALS, AND PREDICTED AND OBSERVED DEATHS FOR THE FIRST DAY OF THE EPISODES AND THE FIRST DAY AFTER THE EPISODES, FOR THE THREE AGE GROUPS.

					Daily Deaths		
Age Group	Period	n	Avg. TSP ($\mu g/m^3$)	Mean of Residuals (deaths/day)	Predicted (deaths/day)	Observed (deaths/day)	Res./ predicted
All							
	Episode	109	71.9	0.874	1.98	2.85	0.44
	After	109	61.3	-0.895	1.68	0.78	0.53
Age 18-64 years							
	Episode	82	70.5	0.642	0.73	1.38	0.87
	After	82	65.7	-0.591	0.68	0.09	0.87
Age GS+ years							
	Episode	120	73.7	0.759	1.61	2.37	0.47
	After	120	62.0	-0.503	1.35	0.85	0.37

Source: Cifuentes and Lave (1996).

deficiency of 0.895 / 1.68 = 53%. There is a large effect in adults of ages 18 to 64 years, with an 87% excess during the first day of a three-day episode and an 87% deficiency in the first day after the episode. The effect for older adults is also large, with a 47% excess during the episode and 37% fewer deaths than expected in the first day after the episode. This strongly suggests that some of the individuals who would have otherwise been expected to die on the first day after the episode may have died 3 days prematurely, on the first day of the episode.

One should also be quite clear about what Table 12-32 does *not* show. The effect of an episode in causing premature deaths is focussed primarily on deaths that occurred within a day or two after exposure, but does not preclude premature deaths that may have occurred more than two days after exposure. There is no estimate here of the cumulative excess of episode-related deaths that were displaced by more than a few days. While acute responses following exposure suggests a cause-effect relationship with at least some short-term displacement of mortality, the

question of long-term excess mortality over times greater than a few days must be addressed by the long-term mortality studies.

The statistical properties of this test merit further research. However, a full investigation of the performance of the test in realistic settings with the more sophisticated time series and GEE methods, including estimation of the harvesting parameter k is beyond the scope of this assessment.

In addition to statistical research, further epidemiologic research is warranted to better characterize the excess deaths in terms of age, cause of death, hospitalization status, prior morbidity, etc. It may be necessary to develop a multistage model, with recruitment of individuals from a healthy stage through one or more stages of morbidity until they reach a susceptible stage at which acute air pollution exposure may cause deaths.

There is, at present, relatively little basis for quantifying the shortening of life in some individuals by periods of months or years using time series data.

12.6.3.4 Adjustments for Meteorological Variables and Other Confounders

There has been only limited progress in developing a systematic approach to the use of weather-related variables in daily mortality or morbidity studies. A variety of ad hoc procedures have been used. While various statistical methods for adjusting daily mortality or morbidity time series for weather effects appear to be successful on a case-by-case basis, there is little understanding of how to do this systematically in a way that appropriately characterizes current knowledge about the relationship between weather, weather changes, and changes in mortality. The empirical adjustments used in most studies are made with little theoretical basis and may be arguable for that reason alone. It is clear that the effects of some variables, such as temperature, are intrinsically nonlinear, and that it may be more useful to define the likelihood of excess weather-related mortality by the presence of clusters of related meteorological variables, such as the synoptic classes suggested by Kalkstein et al. (1994) and used by Pope and Kalkstein (1996) for the Utah Valley. While the synoptic class approach appears promising, it has so far been applied to relatively few cities, and may require further modification to be applicable in a general health effects modelling framework. The problem is that meteorological variables are confounded with other pollutants as well as with PM, so that any misspecifications of the relationship between health effects and weather can provide a distorted set of residual effects to be modelled using air

pollution variables. A causal or mechanistic model could be useful in relating weather, season, pollutant emissions, pollutant concentrations, behavior as it affects exposure, and health endpoints. Remarkably, weather continues to be significantly related to mortality and other health effects, in spite of increasing use of air conditioning.

One interesting possibility in the use of synoptic categories has been demonstrated by Kalkstein et al. (1994). They showed that during the most offensive synoptic weather category, there may be little detectable relationship between PM and excess mortality since most of the excess is attributable to weather. During non-offensive weather categories, however, the excess mortality attributable to PM is readily detected since the weather effect is much smaller and there is a quantitative dose-response relationship between PM and excess mortality.

Weather/climate control between studies has been discussed by Schwartz (1994a,b), Dockery and Pope (1994b) and others as a qualitative issue rather than as a formal numerical evaluation. These papers present global comparisons of RR between cities studied that are labeled as warm or cold cities, based on longer term mean temperature. Since the actual study analysis looked at day to day changes, long-term comparisons of means may not be as informative or appropriate to examine in such a global manner. First, it is not clear that the classification of a city as a warm or cold climate is correct. This dichotomy does not consider moderate climates in a continuum as a factor, so the comparison may not be appropriate. Second, the mortality in the studies is examined on a daily basis as is the temperature. Mean comparison over several months of temperature is an inappropriate control for the study design.

Interrelationships Between Weather, PM, and Mortality

A number of studies have concluded that both extreme weather and high pollution adversely affect mortality. While a majority of this research has examined the independent effect of these stresses on mortality, few studies have successfully separated weather-induced from pollution-induced mortality. This has been especially true in the evaluation of acute mortality. There have been some efforts to evaluate these differential impacts (e.g., Ramlow and Kuller, 1990; Shumway et al., 1988; Schwartz and Dockery, 1992a,b).

Some authors have conducted weather/pollution/mortality evaluations in Steubenville, OH; Philadelphia, PA; London, England; Birmingham, AL; and Utah County, UT as well as other locales. In all of these investigations, they have reported significant associations between human

mortality and PM, and in some cases, the relationship extends to levels well below the current National Ambient Air Quality Standard. In several, they have also alluded to a weather-mortality relationship. For Steubenville, a positive non-linear relationship between both temperature and dew point temperature and mortality was detected. When dummy variables were used to denote hot days, humid days, and hot/humid days, the hot/humid days were a significant predictor of mortality. When seasonal variations were controlled for in their Poisson regression models however, neither temperature nor dew point proved to be significant predictors of mortality (Schwartz and Dockery, 1992b). In a study of British Smoke in London, Schwartz and Marcus (1990) controlled for temperature and humidity and improved the model results significantly over the results of a model with no meteorological variables.

More recent studies indicate that controls for weather may probably not have been adequate to determine true meteorological impacts in the evaluations cited above. Many PM/mortality studies utilize rank-ordered temperatures, squared temperature and dewpoint values, moving averages of temperature, and mean temperatures for groupings of days (see Table 12-33 for further details), which may not provide the detail to detect true weather/mortality relationships. In addition, it is probably not feasible to assume that cities within a wide range of climates demonstrate similar weather/PM impacts on mortality, and there are possibly some regional similarities in response which have not been adequately explored. In a reanalysis of Philadelphia mortality/PM relationships, Schwartz (1994b,c) took a more direct approach to examine the possibility of confounding weather impacts. The reanalysis utilized Hastie and Tibshirani's (1990) "Generalized Additive Model" to detect and control for nonlinearities in the dependence of daily mortality on weather; nevertheless, this study uncovered findings similar to the original Philadelphia study. In addition, Moolgavkar et al. (1995a) assert that the role of weather was improperly evaluated within the Steubenville study, and suggest a more sophisticated evaluation of meteorology in future PM/mortality analyses.

TABLE 12-33. ADJUSTMENTS FOR METEOROLOGICAL FACTORS IN SOME RECENT STUDIES RELATING MORTALITY TO PARTICULATE MATTER

Location Studied and Authors	Pollution Data and Treatment	Mortality Data and Treatment	Weather Data and Treatment	Pollution/ Weather Impact
London Schwartz and Marcus (1990)	British Smoke measurements from 7 stations; logarithmic and square root transformations;	Daily total death counts, including respiratory and cardiovascular causes; sensitivity to filtering	Temperature and RH; grouped plots of temperature and humidity versus mortality; autoregressive model.	British Smoke is significant predictor of mortality; temp/humidity control increased significance, as did autocorrelation adjustment
Philadelphia Schwartz and Dockery (1992a)	TSP samples collected routinely at two monitors; supplemented by sampling every sixth day at several sites; daily means and lags used	Daily total, elderly, <65, pulmonary disease, pneumonia, cardiovascular and cancer mortality; Poisson regression using GEE;	Mean 24 h temp and DP including squared transformation; indicator variables for season, hot, cold, humid, and hot humid days, and year.	Significant TSP association mortality, strongest among elderly and respiratory patients; hot days, mean DP, other weather factors also associated
Steubenville Schwartz and Dockery (1992b)	TSP from one monitor; ranked by levels and sorted into quartiles;	Daily total mortality; Poisson and weather model regressions;	Mean 24 h temp and DP; year as random effect; indicator variables for hot, humid, and hot humid days;	Nonlinear association between TSP and daily mortality; hot humid days associated with daily total mortality;
Utah Pope et al. (1992)	PM_{10} level from one site; up to 7-day lagged moving averages; divided into quintiles used as dummy variables;	Daily total, non-accidental respiratory, cardiovascular, and all other causes of non-accidental mortality; Poisson regression;	Temp and RH; dummy variables used for 10 °F ranges, previous day's temp, 5-day temp moving average, and humidity; linear time trend, random year effect;	Relative risk of death increased monotonically with the mean PM_{10} level for each quintile; also observed when weather controlled;
Erfurt, East Germany Spix et al. (1993)	Suspended particulates; 0-3 day lags; logarithmic transformation;	Daily total mortality; Poisson regression; autocorrelation adjustment for "harvesting"	Daily mean temp, RH, precipitation; indicator variables used for very cold days and hot days for different thresholds, various lags;	Effects of air pollution smaller than influenza and weather effect; significant SO_2
Birmingham Schwartz (1993a)	PM_{10} level averaged from all (1-2) city monitors; divided into quartiles used as dummy variables;	Daily total mortality; Poisson regression using GEE; dummy variables for year and day of week; biannual cycle filters;	Mean 24 h temp and DP; dummy variables same as Utah study, plus cold days; 3-day moving lags;	Significant association between PM_{10} and daily mortality; extremely hot weather also associated with excess mortality; relation to temperature.
Steubenville Moolgavkar et al. (1995a)	TSP from one monitor and SO_2 (two series)	Daily total non-accidental mortality; Poisson regression; with and without GEE; full year and season; serial correlation unimportant.	Mean 24 h temp and DP; indicator variable for hot and humid days; temperature quintiles;	TSP influence on mortality greatly reduced when SO_2 included in analysis; choice of SO_2 series and season had large impact on mortality results.
Philadelphia Wyzga and Lipfert (1995b)	24 h averages of O_3 and TSP from several city monitors; lags of 0 to 4 days tested	Daily non-accidental deaths (non-elderly and elderly); linear filtering; variable for time over entire period in stepwise regression and forced OLS.	Daily maximum temp.; daily change in barometric pressure; dummy variables for winter and seasonality	Strong relationship between temp. and mortality; seasonal adjustments very important; TSP-temp. interaction; most mortality with TSP on hot days.

To further control for weather, Schwartz (1994b,c) stated that the similar responses to air pollution in the "mild" weather of Philadelphia (based on a mean daily temperature of 57 °F) and "cold" weather of London reduce the confounding role of weather. Furthermore, Schwartz (1994b,c) notes that similarity in temperature and humidity on high and low air pollution days

(when different mortality response are noted) "... also would seem to eliminate weather as a potential confounder." However, it is possible that these studies do not remove the total confounding influence of weather, especially because of their dependence on mean temperatures and other meteorological surrogate which may not truly reflect weather variation.

There have been other studies which have attempted to assess the differential impact of PM and weather on acute mortality. For example, Ostro (1993) summarized studies which show strong associations between exposures to PM_{10} and total daily mortality for many urban areas in the United States, Europe, and Canada. In addition, he notes that results are remarkably consistent across regions. However, the impact of weather as a confounding influence is implicitly considered rather unimportant. Ito et al. (1993) showed that daily mortality in London was significantly associated with aerosol acidity levels and British Smoke. Weather played a lesser role, and Ito's work confirms results obtained by others who have evaluated London's mortality/PM/weather relationship (Schwartz and Marcus, 1990; Thurston et al., 1989; Mazumdar et al., 1982). However, it should be noted that London's marine climate is rather benign when compared to many large American cities, as thermal extremes are unusual.

Some studies for cities exhibiting higher climate variation yielded somewhat different results. Wyzga (1978) used the Coefficient of Haze (COH) as a surrogate measure of PM concentration, and determined that high COH values are associated with increased mortality in Philadelphia. However, he recognized the potential impact of extreme weather as well, and noted that heat waves may also be responsible for large numbers of extra deaths. In a recent study by Wyzga in which weather was treated in a more sophisticated manner (Wyzga and Lipfert, 1995a), the impact of ozone concentrations and weather on acute mortality were evaluated and results were compared to TSP. The authors conclude that a determination of ozone and TSP impacts is most difficult because of the influence of confounders, particularly weather. In addition, use of different explanatory models yields disparate results, with pollution impacts ranging, "...from essentially no effect to response similar to that associated with a 10 °F increase in ambient temperature" (Wyzga and Lipfert, 1995a). This evaluation appeared to uncover a synergistic relationship between weather and pollution, as days with maximum temperatures exceeding 85 °F contributed most to the associations between TSP and mortality. Several other studies have uncovered synergistic relationships, and some of these consider pollution to be of secondary importance to weather in affecting acute mortality. Ramlow and

Kuller (1990) found that daily mortality was most closely associated with the daily average temperature of the previous day rather than any pollution measure in Allegheny County, PA. In a study which attempts to determine synergistic relationships between weather and pollution on mortality in Los Angeles, Shumway et al. (1988) determined that mortality is, "...an additive nonlinear function of temperature and pollution, whereas there may be significant interactions present, especially when low or high temperatures are combined with high pollution levels." The authors found that model-predicted average mortality values increased at both temperature extremes when particulate levels were held constant. Two evaluations in the Netherlands found temperature extremes in summer and winter to be primary determinants in mortality variation. Kunst et al. (1993) and Mackenbach et al. (1993) determined that the relationship between temperature and mortality is linear, producing a U-shaped temperature curve, with minimum mortality rates observed between 10 to 15 °C. The Kunst evaluation determined that summer acute mortality is not influenced by variations in air pollution concentration.

Although weather seems to induce mortality increases when temperatures are either very warm or very cold, the impact of weather as a confounder varies seasonally. For example, the impact of weather on acute mortality in winter is much more difficult to evaluate, and thermal relationships are decidedly weaker.

Controlling for Weather in PM/Mortality Analyses: The Use of Synoptic Climatological Methods

A number of procedures have been utilized to control for weather in PM/mortality studies, and although the variety has been great, they generally suffer from common shortcomings. First, many depend on arbitrary decisions to remove extreme weather events from the dataset. The definition of extreme weather to include, for example, days above 90 °F may be proper for a city in the north, but not for a locale further south. Thus, these arbitrary delineations consider weather as an absolute, rather than a relative, factor affecting human health. It is therefore possible that some stressful weather days are not identified, contaminating a PM/mortality dataset which is considered controlled for weather. Second, the use of weather "dummy variables" to control for meteorology within PM/mortality analyses categorizes weather within groupings which may not duplicate meteorological reality. Kalkstein et al. (1991, 1994) propose that the meteorology of a locale is defined by discrete, identifiable situations, which represent frequency modes for

combinations of weather elements. Meteorological delineation that recognize the existence of such modes can be used to control for weather within this context. Third, the use of mean weather elements (e.g., mean daily temperature) does not permit a proper evaluation of, or control for, daily weather extremes. Finally, most all consideration of weather in PM/mortality studies are thermal (temperature), and, less frequently, moisture (humidity) dependent. This creates a potential weather control problem, as certain meteorological phenomena, such as stormy situations associated with mid-latitude cyclones, are not associated with thermal extremes, yet may be very important contributors to acute mortality (Kalkstein et al., 1994). These are rarely controlled for in PM/mortality studies, as they cannot be identified on the basis of temperature and humidity.

A completely different approach is that adjustment for weather-related variables is needed only insofar as it provides a basis for removing potential confounding of excess mortality with PM and other air pollutants, and that any empirical adjustment for weather is adequate. One of the most completely empirical methods for adjusting daily time series data for covariates is by use of nonparametric functions, such as LOESS smoothers, generalized splines, or generalized additive models (GAM), as demonstrated in Schwartz (1994d,e,f,g,h; 1995a,b); and Schwartz and Morris (1995). These are empirically satisfactory and may provide a better fit to data than synoptic categories, but at the loss of a basis for defining weather "episodes" as a characterization of duration of exposure.

Application of synoptic climatological procedures to control for weather has the potential to compensate for these difficulties and add further insight by defining an entire set of meteorological conditions which lead to increases in mortality. Many U.S. cities tend to be especially affected by a single type of "offensive" summer air mass associated with unusually high mortality (e.g., Philadelphia, Table 12-34). This "moist tropical" air mass in

TABLE 12-34. MEANS AND STANDARD DEVIATION FOR SUMMER AIR MASSES IN PHILADELPHIA

	Total Mortality					Elderly Mortality			
Air Mass Category Number	Mean 3 PM Temperature	Mean Mortality[a]	Standard Deviation	% of Top 50 Mortality[b]	% Top 50 % Frequency[c]	Mean Mortality	Standard Deviation	% of Top 50 Mortality	% Top 50 % Frequency
1	77.0	-4.11	12.87	2.00	0.14	-0.91	9.99	0.00	0.00
2[d]	89.0	8.89	16.14	46.00	3.77	6.72	12.58	46.0	3.79
3	82.4	1.63	12.82	14.00	1.27	1.59	10.76	14.00	1.28
4	79.0	-4.43	10.19	0.00	0.00	-2.82	9.33	2.00	0.23
5	82.6	-2.57	11.14	4.00	0.45	-1.36	11.10	4.00	0.45
6	85.0	3.92	16.83	14.00	1.99	3.84	13.77	10.00	1.42
7	80.6	0.70	11.82	2.00	0.14	0.52	10.41	4.00	0.67
8	85.5	2.47	12.49	8.00	1.08	2.70	9.88	10.00	1.33
9	74.7	-4.49	12.53	0.00	0.00	-2.56	10.39	2.00	0.31
10	83.6	0.13	11.80	6.00	1.07	1.28	10.86	4.00	0.67

[a]Values are evaluated against a baseline of 0.
[b]Represents the percentage of top 50 mortality days within a particular synoptic category.
[c]Ratio of percentage of top 50 days within the synoptic category over the seasonal frequency of the category. A number greater than one indicates that a larger proportion of days in the synoptic category are among the top 50 mortality days than might be expected based on the frequency of the category.
[d]"Offensive" category.

Source: Kalkstein (1993).

Philadelphia, possessing the highest maximum and minimum temperatures, was also associated with the greatest standard deviation in mortality of all air masses evaluated. Thus, although many days within the offensive air mass were associated with high mortality totals, a number of days showed little mortality increase. The greatest daily mortality totals during moist tropical air mass incursions occurred as part of a lengthy string of consecutive days of the air mass, and when minimum temperatures were particularly high. This type of information may be important when controlling for weather in PM/mortality analysis.

Offensive air masses which lead to mortality totals significantly higher than the long-term baseline have been identified for a number of U.S. cities (Table 12-35). In most cases moist tropical air masses were deemed offensive (especially in the East), but the very oppressive "dry tropical" air mass was often associated with the greatest increases in mortality, especially in New York, St. Louis, Philadelphia, and in southwestern cities (Kalkstein, 1993b). In some cases, daily mortality totals are over 50% above the baseline (World Health Organization, 1996). The air mass analyses support the notion that acute mortality increases only after a meteorological threshold is exceeded. This threshold is not only temperature dependent; it represents an overall meteorological situation which is highly stressful. It is noteworthy that most cities demonstrate only one or two offensive air masses which possesses meteorological characteristics exceeding this threshold.

In a PM study where stressful weather days are removed from the data base, synoptic categorization provides an efficient means to remove such days with greater security that very few meteorologically offensive days are contaminating the remaining dataset. In studies where weather is stratified based on certain meteorological elements, synoptic categorization allows for a meteorologically realistic control, and may be preferable to the use of arbitrary dummy variables when identifying meteorological conditions with an elevated mortality risk.

The Effect of Different Weather and Time Trend Model Specifications on Concentration-Response Models for PM_{10}

A recent study by Pope and Kalkstein (1996) allows detailed assessment of the effects of the substantially different approaches to modeling conentration-response and weather variables. The original analyses and reanalyses of the Utah Valley data by Samet et al. (1995) use quintiles of PM_{10} as the indicator. The reanalyses reported by Pope and Kalkstein as Models 1-8 used a linear model for 5-day moving average PM_{10}, and

TABLE 12-35. DAILY EXCESSIVE MORTALITY (SUMMER SEASON) DURING OFFENSIVE AIR MASSES

City	Offensive Air Mass	Mortality Above Baseline[a]	City	Offensive Air Mass	Mortality Above Baseline[a]
Birmingham	MT	+2	Kansas City	DT	+5
Phoenix	MT	+1		MT*	+3
Los Angeles	MT	+9	St.Louis	DT	+15
	DM	+3		MT*	+2
Riverside	DT	+2	Newark	DT	+6
San Francisco	DT	+9		MT*	+4
Hartford	MT	+3	Buffalo	MT*	+3
Tampa	MM	+1	Nassau, NY	DT	+6
	MT*	+3		MT*	+5
Atlanta	DP	+4	New York	DT	+49
	MT*	+3		MT*	+30
Chicago	DT	+9	Cincinnati	MT*	+2
	MT*	+14	Columbus	MT*	+3
Indianapolis	MT*	+3	Portland	DT	+5
Louisville	MT*	+2	Philadelphia	DT	+32
Boston	MT*	+8		MT*	+10
Baltimore	MT*	+5	Providence	MT*	+7
Detroit	DT	+10	Memphis	DT	+3
	MT	+8		MT*	+1
Minneapolis	DT	+4	Dallas-Ft.Worth	DT	+3
	MT*	+6			
			Houston	DT	+8
			San Antonio	DT	+1

[a]Mean daily deaths above the long-term baseline.
Air Mass Abbreviations: MT = Moist Tropical; DM = Dry Temperate; DT = Dry Tropical; MM = Moist Temperate; DP = Dry Polar. Asterisks denote a particularly offensive subset of MT.

Source: Kalkstein (1993b).

8 different weather models: (1) no adjustment; (2) indicator variables for 20 seasons (1985-1990); (3) indicators for 20 seasons, and indicators for for quintiles of temperature and relative humidity; (4) indicators for 20 seasons, and indicators for 19 synoptic weather categories; (5) linear time trend,, and indicators for 19 synoptic categories; (6) LOESS smooth of time (span = 10 percent of days); (7) LOESS smooths of time (span = 10 percent of days), temperature (span = 50 percent of days), and relative humidity (span = 50 percent of days); (8) LOESS smooth of time (10 percent of days), and indicator variables for 19 synoptic categories. The results are shown in Table 12-36. The results are relatively insensitive to the form of time trend and adjustment for weather

variables, with RR for 50 μg/m3 increments in PM_{10} varying only from about 1.058 (Model 2) to 1.077 (Model 7) for total mortality, all of them statistically significant. The pulmonary mortality models are somewhat more sensitive to the form of the covariate adjustments, with RR for 50 ug/m^3 ranging from 1.132 (Model 6) to 1.221 (Model 7); Model 2 shows only a marginally significant PM_{10} coefficient, the others significant one-tailed (Models 3 and 4) or two-tailed. The cardiovascular mortality models have RR ranging from 1.076 (Models 3 and 7) to 1.116 (Model 1), with Model 3 one-tailed significant and all other models showing a significant PM_{10} effect on cardiovascular mortality. While the authors comment that other communities may show greater sensitivity to the statistical methods for adjusting for time trend and weather, the relative lack of sensitivity of the estimated PM_{10} effect over a very wide range of models is noteworthy.

Table 12-36 also shows subset models corresponding to Models 7 and 8. Cold season models called Models 9 and 11 by Pope and Kalkstein (1996, Table 4) consist of Models 7 and 8 respectively, limited to the months of October to March. Intra-seasonal differences are adjusted by LOESS smoothers of time, and daily weather variation either by LOESS smoothers of temperature and relative humidy (Model 9) or by indicators for synoptic categories. Total mortality is highly significant in either case (1.070 for Model 9 and 1.059 for Model 11). Pulmonary mortality is higher (1.145 for Model 9 and 1.120 for Model 11) and marginally significant. Cardiovascular mortality has RR = 1.062 in Model 9 (not significant) but RR = 1.075 (significant) in Model 11. The corresponding Models 10 and 12 for the warm season (April-September) shows higher RR effects for total and pulmonary mortality, but the effects are not at all statistically significant. The lower statistical significance may reflect the halving of the sample size in these data sets, since the effect size estimates must be similar to those obtained by averaging the whole-data analyses across the corresponding seasons, with cold season = fall + winter approximately, and warm season = spring + summer approximately.

Pope and Kalkstein (1996) also show four nonparametric smooth regression plots corresponding to Models 1, 6, 7, and 8, respectively. All of the models using a nonparametric regression for daily mortality on PM_{10} are approximately linear, showing

TABLE 12-36. EFFECTS OF DIFFERENT MODELS FOR WEATHER AND TIME TRENDS ON MORTALITY IN UTAH VALLEY STUDY

Model Identity	Time Model	Weather Model	Relative Risk for PM_{10} 50 $\mu g/m^3$		
			Total Mortality	Pulmonary Mortality	Cardiovascular Mortality
Base I	-	-	1.076 (1.044, 1.109)	1.198 (1.035, 1.386)	1.094 (1.019, 1.174)
Base II	-	-	1.083 (1.030, 1.139)	1.215 (1.049, 1.408)	1.094 (1.020, 1.174)
1	None	None	1.074 (1.032, 1.118)	1.185 (1.056, 1.331)	1.116 (1.054, 1.181)
2	20 seasons	None	1.058 (1.002, 1.118)	1.133 (0.963, 1.333)	1.081 (1.000, 1.169)
3	20 seasons	Quintile	1.062 (1.003, 1.124)	1.150 (0.972, 1.361)	1.076 (0.992, 1.167)
4	20 seasons	Synoptic	1.068 (1.009, 1.130)	1.169 (0.988, 1.382)	1.090 (1.005, 1.183)
5	Linear	Synoptic	1.068 (1.020, 1.118)	1.183 (1.032, 1.356)	1.100 (1.030, 1.175)
6	LOESS	None	1.059 (1.017, 1.102)	1.131 (1.006, 1.273)	1.085 (1.024, 1.150)
7	LOESS	LOESS	1.077 (1.028, 1.129)	1.221 (1.063, 1.402)	1.076 (1.006, 1.152)
8	LOESS	Synoptic	1.068 (1.021, 1.117)	1.166 (1.018, 1.335)	1.099 (1.029, 1.173)
9	Cold season, LOESS	LOESS	1.070 (1.015, 1.129)	1.145 (0.981, 1.337)	1.062 (0.984, 1.146)
10	Warm season, LOESS	LOESS	1.112 (0.918, 1.346)	1.529 (0.813, 2.877)	1.053 (0.789, 1.404)
11	Cold Season, LOESS	Synoptic	1.059 (1.009, 1.111)	1.120 (0.971, 1.291)	1.075 (1.003, 1.153)
12	Warm season, LOESS	Synoptic	1.091 (0.947, 1.258)	1.394 (0.794, 2.577)	1.024 (0.780, 1.343)

Source: Pope and Kalkstein (1996)

some suggestion of nonlinear structure between roughly 60 and 100 μg/m3 PM_{10}, but in no case suggesting a threshold or consistent flattening of the concentration-response relationship at any PM_{10} concentration. The authors note that a chi-squared test comparing each non-parametric regression model for PM_{10} with the corresponding linear model shows no statistically significant deviation from linearity.

Samet et al. (1996b) have recently published another study of different methods for estimating the modifying effects of different weather models on the relationship of TSP and SO_2 to total mortality in Philadelphia from 1973 to 1980. The models included the original Schwartz and Dockery (1992a) weather specification, a nonparametric regression model, LOESS smoothing of temperature and dewpoint, and Kalkstein's Temporal Synoptic Index (TSI) or Spatial Synoptic Category (SSC) models. The first three methods allowed the weather model to be adjusted so as to provide an optimal prediction of mortality, whereas the latter two models were based completely on external criteria and the classification of days by SSC or TSI categories was not adjusted to improve prediction of mortality. The authors conclude the "... the association between air quality as measured by either TSP alone, SO_2 alone, or TSP and SO_2 together, cannot be explained by replacing the original Schwartz and Dockery weather model with either a nonparametric regression, LOESS, or by synoptic categories using either Kalkstein's TSI or SSC systems. In addition, there is little evidence in the Philadelphia total mortality data to support the hypothesis that the pollution effects are modified by the type of weather conditions as measured either by TSI or by strata created from the predicted weather-induced mortalities using the Dockery and Schwartz model or the LOESS model. ... We did not fine variation of the effect of pollution across categories of weather." Their results are not shown here.

Additional studies systematically evaluating the differential effects of PM and other pollutants by weather category would be of interest. The Philadelphia study by Samet et al. (1996b) used only TSP and SO_2, whereas the Utah Valley study by Pope and Kalkstein (1996) did not look at the effects of weather as a modifier with other pollutants as well as PM_{10}.

Confounding by Epidemics

Concern exists that the increased incidence of illness or mortality associated with changes in air pollution during the winter season may not indicate a causal relationship because of confounding influences of contagious illnesses epidemics. Infectious respiratory illness (e.g., the "flu") strongly influences mortality. An underlying or contributing cause for changes in air pollution or in contagious illness may be weather changes. Confounding due to epidemics may be adjusted statistically to some extent by use of filtering, but this is at best suitable for time series with a normally distributed response, and filtering of time series may perform better when there is some recurrent medium-to-long wave pattern to outbreaks of the disease in a given population. Without some recurrence pattern, filtering may only eliminate evidence of longer-term persistence of health effects related to air pollution. Close inspection of the time course of infectious respiratory illness outbreaks in populations reveals that outbreaks do not appear on a regular schedule from year to year (Henderson et al., 1979a,b; Murphy et al., 1981; Chapman et al., 1981; Denny et al., 1983). In any given year, a number of important respiratory pathogens may not appear at all in a given population. Thus, fixed-cycle curve-smoothing techniques may not accurately describe the time course of respiratory illness outbreaks in populations. Several investigators have subsequently used long-term nonparametric methods such as loess smoothers or generalized additive models (GAM) to adjust mortality series for aperiodic fluctuations that may include time-extended outbreaks of respiratory disease (Pope, 1994; Schwartz, 1994b,c, 1995b).

It is sometimes possible to evaluate the effect of epidemics on health outcome time series by comparison with adjacent communities. Pope (1991) evaluated the possible effect on hospital admissions of contagious illnesses such as influenza (which is known to cause a substantial number of deaths in the elderly) and respiratory syncytial virus (RSV, which affects a substantial number of children and is often mistakenly diagnosed as influenza). There was particular interest in the possibility that infectious diseases occurred more often during the winters when the Utah Valley steel mill was open, and less often during the winter when the steel mill was closed, purely by chance. Pope writes that "The few diagnoses where the agent of disease was specified limited opportunities to directly observe epidemics of any specific infectious agent. Bronchitis and asthma admissions for preschool-age children were more than twice as high in Utah Valley during periods when the mill was operating than when it was closed. The potential of highly localized

epidemics of contagious respiratory disease that were correlated coincidentally with the operation of the steel mill cannot be completely ruled out. If the association were strictly spurious, however, the same correlation would probably be observed in neighboring communities unaffected by the mill's pollution. Such correlations were not observed."

The ability to directly observe diagnosed cases of influenza or RSV would allow a direct adjustment of health outcome time series for community-wide incidence of occurrence of the disease, which could in turn be exacerbated by co-occurring air pollution. Some progress in obtaining data on outbreaks of influenza-like illnesses (ILI) may be possible using recently established data bases, such as the CDC volunteer physician surveillance network. Evidence exists that these 140 family physicians make good sentinels for epidemics of ILI (Buffington et al., 1993). Data are provided to CDC on a weekly basis, which seems appropriate to the level of filtering that may be needed to adjust daily time series of health outcomes and air pollution for co-occurring respiratory diseases.

Confounding: Is It a Real Problem?

In developing criteria for assessing epidemiologic studies, we have paid a great deal of attention to the potential confounding of PM effects on human health with the effects of other agents that are associated with PM. Confounding has both conceptual and technical aspects. We will first discuss some of the conceptual aspects.

There are three distinct options by which an analyst can deal with confounding in an epidemiology study: (1) control; (2) avoid; or (3) adjust by analysis. It is obviously preferable to control confounding by designing a study in such a way that all of the potential confounding effects are anticipated and avoided. If confounding is unavoidable, then all levels of the nominal causal agent (PM) and its confounding factors should be included in the study, preferably in a balanced design so as to simplify the analyses of the data. Since the PM studies are all observational studies, study design rarely allows a representative sampling of all levels of all factors. For example, in a city or region where there are large stationary sources that burn fossil fuels containing sulfur, both PM and SO_2 are likely to be high at the same time or low at the same time, being governed by similar patterns of generation and dispersion. Likewise, if mobile sources burning fossil fuel are the primary source of PM in a region, then PM during the summer is likely to be associated with some or all of the following factors: high temperatures, low wind speed,

high concentrations of ozone, CO, and airborne nitrates. Therefore, avoiding situations in which confounding occurs is not usually an option.

However, there are some situations in which certain kinds of confounding are minimized. One example occurred in the Utah Valley studies. During the year that the mill was closed due to a strike, PM emissions from the mill were greatly reduced, but not quite eliminated since the coke ovens were banked during the closure, and not shut down. The years before and after the closure were years with high PM_{10} concentrations and typical weather. The year during the closure had generally typical seasonal weather, but much lower PM_{10} levels. Hence, confounding between PM_{10} and weather was relatively minimal during the study. Other studies by Pope et al. (1991) and Pope (1989) in surrounding counties showed little evidence of any change in the incidence of respiratory infections during the year of closure, so that confounding of winter health effects with epidemics of respiratory infection seems unlikely. Other pollutants were at low levels even when the mill was operating, particularly SO_2. Summer levels of ozone were high enough to merit covariate adjustment, but had little effect on the estimated RR for various health effects of PM_{10}.

In general, the potential for confounding of PM effects with the effects of other air pollutants is regionally distributed, with sulfates forming a higher percentage of particle mass in areas of the eastern U.S. and Canada, and nitrates a larger percentage than sulfates in the western U.S. and Canada. Thus, the potential for confounding with $SO_4^=$ and with SO_2 is greater in studies in eastern states, and the potential for confounding of PM effects with effects of NO_x, and (presumably) with other air pollutants such as CO and O_3 that are generated largely by mobile sources, varies with location. Likewise, there is some confounding of health effects of PM with health effects from weather, since weather conditions may affect both generation of PM and its atmospheric dispersion (that is, concentration). For this reason, it may also be helpful to take a multi-city or multi-study perspective in comparing the effects of potential confounding variables on RR for PM.

Schwartz (1994c,d; 1995a,b) has emphasized a multi-study and multi-endpoint perspective from several points of view. We believe that comparisons of study results across different studies is very useful, but the approach still leaves some unresolved questions about confounding. For example, a completely factorial design controlling for effects of weather and co-pollutants might require finding studies in both "hot" and "cold" cities, in "wet" and "dry" cities, in cities with "high" SO_2 and "low" SO_2, with "high" O_3 and "low" O_3. Thus, even a simple factorial design

would require comparisons of at least $2^4 = 16$ cities, counties or SMSA's. Since the variables used in describing the cities are numeric, combining the results would be more appropriately done using a "meta-regression" in the same sense as in the cross-sectional analyses done for the long-term exposure studies, rather than a "meta-analysis". Meta-analyses are discussed below. In general, there have not been enough reported studies to do this "meta-regression". There are also problems in defining levels of weather effects, since Kalkstein et al. (1994) have shown that thresholds for excess mortality from high temperatures are different in different cities. That is, a "high" temperature in Minneapolis-St. Paul or Seattle, may not have the same effect in Birmingham or Los Angeles, and that differences may depend on other weather variables and on climate conditions. This approach also shares another concern about population-based cross-sectional studies, that populations in different cities are demographically different in ways that affect population-based health outcomes. Even the measure of effect size that we have used for most of our comparisons, relative risk of health outcome for PM or other factors, is relative to a base rate for the health outcome that one would expect to differ somewhat among different populations in different cities.

Avoidance of confounding is also possible for some co-pollutants. Gaseous chemical compounds such as SO_2, CO, and O_3 are likely to have very similar effects in different conditions, everything else (such as temperature and humidity) being equal. When levels of these pollutants are very low, such as SO_2 in most western studies, there is virtually no chance that these pollutants have a causal effect on health endpoints such as mortality and hospital admissions. While such effects cannot be absolutely excluded, the fact that they are often found at levels very far below the NAAQS should control their contribution to some extent.

In spite of these concerns, the general similarity of RR estimates for acute mortality in different studies and the large differences in potential confounding variables among the studies, along with the similarity of RR to that found in studies where confounding effects seem relatively minimal, adds a great deal of credibility to the conclusion that the PM mortality effects are real, and similar in many locations, even if their magnitude is small and somewhat uncertain. This is not to say that there is no confounding with co-pollutants, particularly where pollutants such as SO_2 are generated by the same process that generates PM. Differences in RR for hospital admissions are somewhat greater, possibly reflecting differences in demographic factors or regional differences in hospital admissions criteria, but for similar reasons these estimates are not

so seriously confounded in every study as to preclude concluding that, in some studies, there are real increases in hospital admissions rates for the elderly, and for certain classes of respiratory and cardiovascular conditions.

Control of Confounding By Covariate Adjustment

For most of the short-term studies, there is some unavoidable confounding with co-pollutants, with weather, and possibly with other medium-term and long-term events such as epidemics and seasons. Different model specifications of some studies in Section 12.3 were compared at length in Section 12.6.2. Weather variables and temporal variations over times longer than a few weeks can be adequately modeled using any of several approaches discussed above, such as polynomials, sinusoids, indicator variables for each month and year, indicators of synoptic climatological categories, nonparametric smoothers or generalized additive models, or high-pass filtering for Gaussian models. Careful examination of residuals for Poisson or Gaussian models have found that a large number of alternative models can provide regression residuals or Poisson expectations apart from air pollution variables that are independent of season, so that seasonal subsetting of time series data in short-term studies may not be necessary for adequately adjusted models. Sometimes, as in analyses of the London mortality series (U.S. Environmental Protection Agency, 1986a; Schwartz and Marcus, 1990), only seasonal monitoring data are available, but one should not make a virtue of necessity by subsetting time series, since statistical tests to detect PM effects of the magnitude currently observed in the U.S. require long series of data, roughly at least 800 values. Apart from this sample size requirement, different methods for adjusting for weather and time trends provided adequate levels of adjustment to control for these factors. In addition to controlling confounding with air pollution, it is also important to fit very good models for weather and time trends in time series data, however, so as to help reduce residual variability in daily response data to the limiting or irreducible Poisson minimum variance, which is equal to the expected number on that day.

12.6.3.5 Adjustments for Co-pollutants

Not all studies contain data on the major co-pollutants, and a wide variety of approaches has been used to assess the importance of these co-pollutants as predictors of health effects that compete with PM in terms of explanatory power. Studies in which no other co-pollutant is

assessed probably over-estimate the PM effect, but the use of a large number of more or less closely related pollutants to predict the health outcome almost guarantees that the statistical significance and size of the PM effect will be under-estimated. So far, few of these studies have used effective diagnostic techniques or alternative methods for dealing with correlated (e.g. multicollinear) predictor data.

Earlier discussion has indicated that other pollutants such as SO_2 are factors that play a role in modifying the relationship between PM and mortality when they are incorporated into models examining these relationships such that the RR is usually smaller. Other pollutants such as O_3 and CO also need to be considered. Indeed as more studies incorporate these other pollutants into the studies, concern for the role they play becomes more important. This applies to hospitalization studies where possible relationships with CO may be evident. The biological plausibility of CO and sudden death is established. The earlier major air pollution episode events in London involved relatively high levels of CO (Commins and Waller, 1967). Section 12.6.2 conducted an intense examination of the roles of copollutants with a focus on SO_2 but also O_3 and CO to determine what roles these copollutants play and what summary statements are possible to allow conclusions about PM effects to be stronger.

One of the more difficult problems in interpreting the analyses of the studies discussed here is that of separating the effects of several air pollutants. These pollutants are often fairly highly correlated, and the correlation is often causal, in that several pollutants may be emitted by the same mix of sources in a community, or that one pollutant is a precursor to another pollutant or to a component of that pollutant, such as the fractions of sulfates and nitrates in PM that are secondary pollutants formed from SO_2 or NO_x. There have been a number of studies in which several different model specifications were tested, involving PM as the only air pollutant, versus PM and other pollutants used jointly in the model. In many studies, such as TSP in Philadelphia (Schwartz and Dockery, 1992a) there was little effect of SO_2 on the RR for TSP, whereas other authors have found that SO_2 appeared to modify the TSP effect in some seasons, using a similar approach and data set, but with less comprehensive adjustment for weather variables and time trends. There are two ways in multi-pollutant models can cause differences in interpretation from a single-pollutant model: (1) the correlation between PM and the other pollutant(s) is (are) sufficiently high that the effect or health outcome attributable is shared among the pollutants and the individual RR for any one pollutant may be seriously biased. Measurement error in pollutants

or other covariates may also bias the result, not necessarily towards the null, and the most poorly measured exposure covariate is usually the one that is driven towards no effect; (2) parameter variance estimates are seriously inflated among the entire group of nearly collinear covariates, increasing estimated standard errors and the width of the confidence intervals for the RR estimates and thereby also attenuating their apparent statistical significance.

Collinearity diagnostics have been developed for Gaussian OLS regression models (Belsley et al., 1980) and are implemented in most modern statistical programs. Analogous methods for Gaussian, logistic, or Poisson time series models are less well developed. Most programs allow calculation of the correlation coefficient between estimates of regression parameters (denoted B) based on the asymptotic covariance matrix. However, as noted in Table 12-5, correlation of the B's was given in only two out of ten studies relating acute mortality to PM_{10}. Pollutants with similar patterns and effects can be identified by B-correlation values close to -1. Numeric diagnostics for confounding of co-pollutants could be easily included in reports of long-term studies, many of which use Gaussian OLS linear or nonlinear regression methods for which these diagnostics are readily calculated.

Some investigators have noted that similarity of PM regression coefficients in single- and multiple-pollutant models is sufficient to show that PM is not confounded with the other pollutants. This is not the whole story, since there is a possibility that the B coefficient or RR for PM is unchanged, but the confidence limits are much wider because of the variance inflation of the parameter estimate for collinear pollutants. When the RR estimate for PM is relatively unchanged and there is little increase in the width of the confidence interval, then one can say there is little evidence of confounding. This has been done in a number of analyses discussed in this section, for example in the Utah Valley mortality study as shown in Figure 12-21. The RR estimates for the summer season and the width of the confidence intervals for PM_{10} are similar without ozone in the model, with daily average ozone, or with maximum daily one-hour ozone as the co-pollutant. The summer PM coefficient, with or without ozone, is similar to the winter value, when ozone levels were so low as to have little probable effect on mortality, which illustrates both covariate adjustment and confounder avoidance strategies in the same study.

There is some question about whether the confounding of certain co-pollutants such as PM and SO_2 should be regarded as true confounding when one pollutant is part of a causal pathway from pollution source to pollution monitor (Rothman, 1986). Our assessment of probable causal

pathways in a hypothetical multivariate model relating source emissions, weather, air pollution, and health outcomes is shown in Figure 12-35. This could serve as a framework for a statistical analysis in which the direct and indirect effects of air pollutants and other factors could be disentangled using substantive scientific hypotheses and data.

Concentration-Response Surfaces for Two or More Pollutants

A recent study by the Health Effects Institute (Samet et al., 1995) shows how additive and interactive models can differ. An example of an additive linear model is one in which s(x) = bx and S(x) = dx, so that

$$\log(E(Y)) = XB + b\ PM + d\ OP$$

is constant along any line in which b PM + d OP is constant. When Samet et al. fitted a two-dimensional smoothing model to Philadelphia mortality counts against PM = TSP and OP = SO_2, where the general form of the model was defined by a two-dimensional nonparametric smoothing function ss,

$$\log(E(Y)) = XB + ss(TSP, SO_2),$$

the resulting models differed substantially from an additive linear form and showed evidence of very strong non-linearity as well as non-additivity.

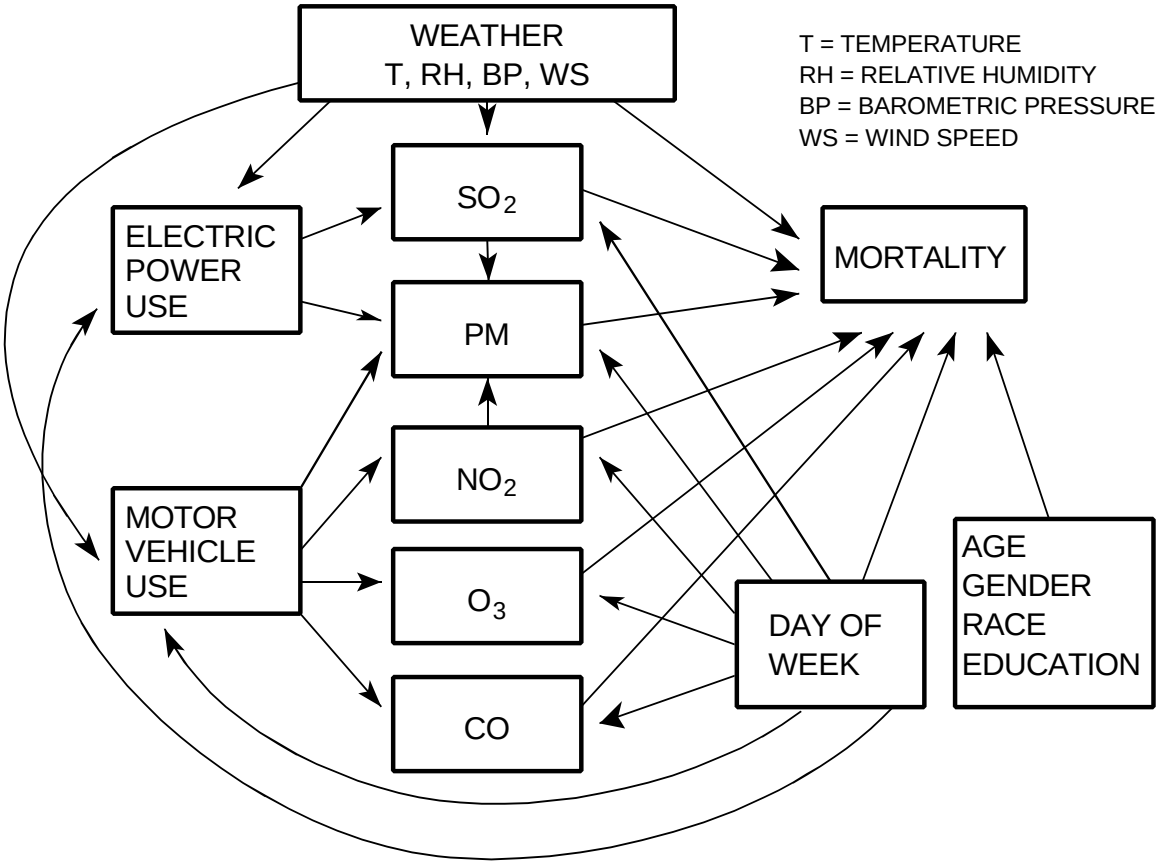

Figure 12-35. A conceptual model of sources and pathways for air pollution health effects such as mortality, including a causal model of potential confounding by co-pollutants. No attempt is made to differentiate strength of evidence for each pathway.

In general, most papers have provided very little empirical basis for the reader to assess the adequacy of the fitted model, especially for analyses involving copollutants. The most data-driven display would consist of a three-dimensional scatterplot, whose axes are the PM index, the copollutant, and the response variable (mortality). The HEI report comes closest to this by presenting three-dimensional surfaces showing the *smoothed* or fitted mortality response versus TSP and SO_2 for the 1973 to 1980 Philadelphia data set (see Figures 12-36 and 12-37). The smoothed surfaces are based on LOESS smoothers whose bandwidth includes 50 percent of the data, reflecting a substantial degree of smoothing of daily mortality counts. The smoothed actual data surface falls considerably above the linear model

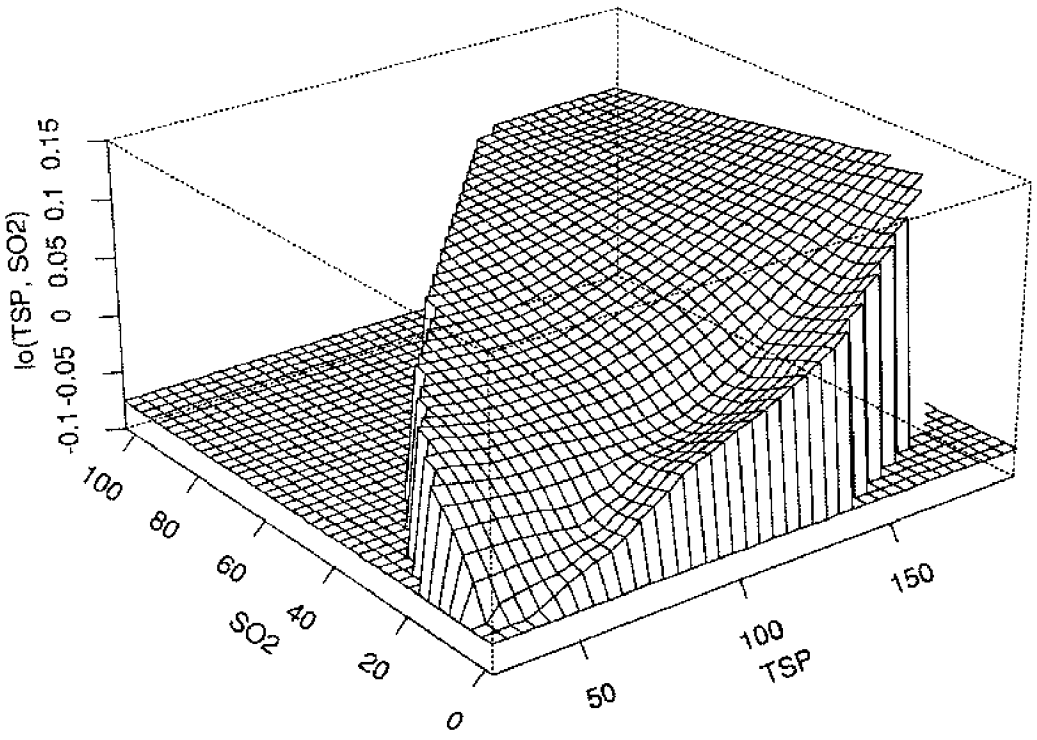

Figure 12-36. Smooth surface depicting relative effects of sulfur dioxide (SO_2) and total suspended particles (TSP) levels on total mortality for Philadelphia, 1983 to 1988. Surface was estaimated from a generalized additive model (Hastie and Tibshirani, 1990) using a LOESS smoother (bandwidth 50% of data, 10.2 degrees of freedom). Deviations from a plane surface suggest a nonlinear concentration-response function.

Source: Samet et al. (1995).

surface for TSP greater than about 100 $\mu g/m^3$ and almost all SO_2 levels above 20 ppb. Below about 75 $\mu g/m^3$ TSP, the plane surface generally lies above the smoothed data surface. This suggests that there is a very complex pattern of dependence on the joint values of TSP and SO_2 that is not adequately captured by an additive linear model.

A somewhat different way of looking at the results from Figure 12-36 is shown in Figure 12-38. Figure 12-38 shows the contours of the same two surfaces projected onto the plane with TSP and SO_2 values for each day in the data set. The contour lines represent TSP and SO_2 combinations for which the estimated excess risk of mortality in Philadelphia is equal to the value shown. The parallel lines are estimates from the regression plane in the additive linear model. The curved contours represent smoothed estimates from the LOESS

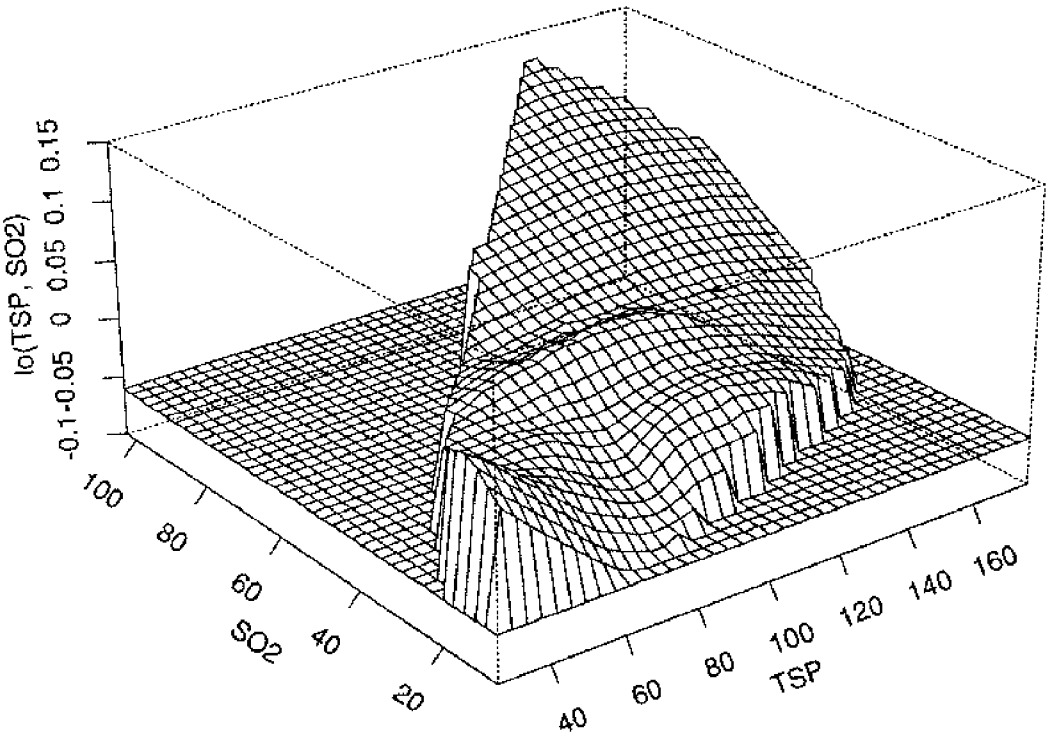

Figure 12-37. Smooth surface depicting Philadelphia mortality in winter relative to sulfur dioxide (SO_2) and total suspended particles (TSP), 1973 to 1980. Surface was estimated from a generalized additive model (Hastie and Tibshirani 1990) using a LOESS smoother with 9.6 equivalent degrees of freedom, controlling for temperature, dew point, and day of the week.

Source: Samet et al. (1995).

smoothing model and may be thought of as simplified representations of the data. The two sets of curves appear quite different, and in fact the difference in deviance of the mortality counts between the LOESS model (with 10.2 equivalent degrees of freedom) and the additive linear model (with 2 degrees of freedom) is 28.0 with 8.2 degrees of freedom, which is a statistically significant difference at level P = 0.01 after adjustment for overdispersion of the mortality counts (Samet et al., 1995, p. 31).

The nature of the nonlinear and nonadditive response surface provides additional information. If the contour lines in Figure 12-38 are roughly parallel to the horizontal axis (TSP), then the figure suggests that mortality is changing in relation to the variable on the vertical axis (SO_2), as is suggested for TSP less than about 75 $\mu g/m^3$. If the contour lines in Figure 12-38 are roughly parallel to the vertical axis (SO_2), then the figure suggests that

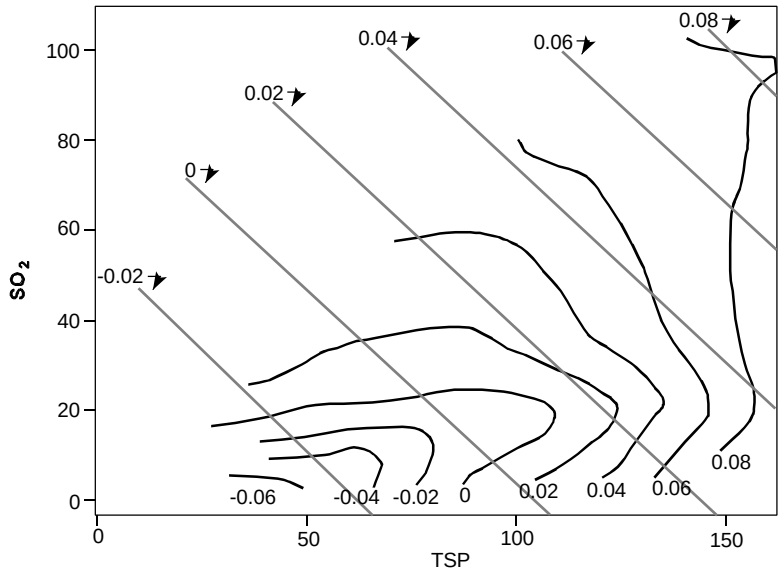

Figure 12-38. Curved contours depicting the excess risk of total mortality in Philadephia, by season, for 1983 to 1988. Straight lines show the excess risk from an additive linear model fitted to the same data, which exhibits significantly inferior goodnesss of fit relative to the GAM model.

Source: Adapted from Samet et al. (1995).

mortality is changing in relation to the variable on the horizontal axis (TSP), as is suggested for TSP greater than about 125 $\mu g/m^3$. The contours change orientation between 75 and 125 $\mu g/m^3$ TSP. It is clearly not correct to conclude from the additive linear model that one pollutant is always (or never) a better predictor of excess mortality in Philadelphia than is the other pollutant.

Seasonal differences also seem to play an important role. Figures 12-39 through 12-42 show analogous results from the HEI report for spring, summer, fall, and winter 1973 to 1980 data. In Figure 12-39 (spring), the nonparametric contours for TSP greater than about 125 $\mu g/m^3$ are roughly parallel to the straight lines from the additive linear model but spaced irregularly, suggesting an additive but somewhat nonlinear model for TSP and SO_2 in this range. For TSP below about 75 $\mu g/m^3$, there seems to be little relationship of mortality of TSP.

The summer results are shown in Figure 12-40. For TSP greater than about 110 $\mu g/m^3$ and SO_2 less than about 20 ppb, the nonparametric surface contours are roughly parallel to the additive linear model contours, but more closely spaced. For TSP greater than about

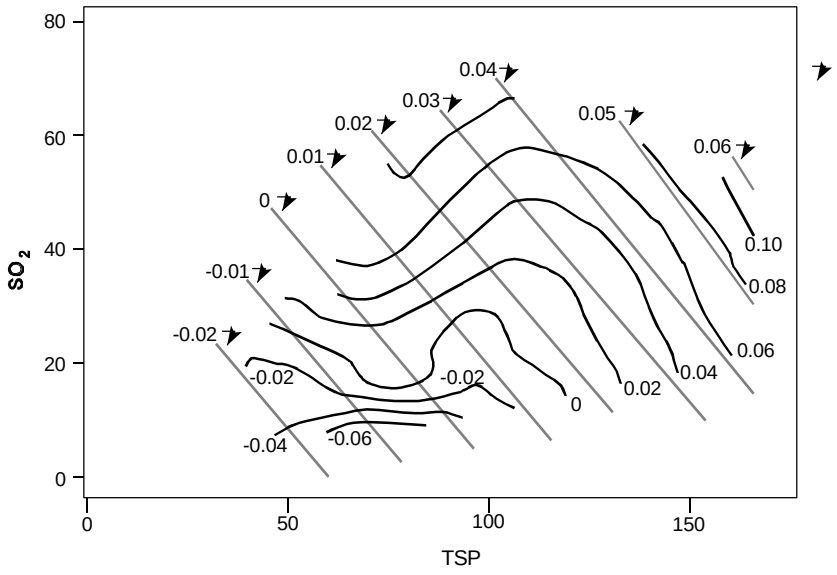

Figure 12-39. Contours depicting the fractional change in Philadelphia mortality in spring by levels of total suspended particles (TSP) and sulfur dioxide (SO_2). Straight lines show contours predicted by an additive model. Contours predicted by LOESS with 10.2 equivalent degrees of freedom are shown in the curved lines.

Source: Adapted from Samet et al. (1995).

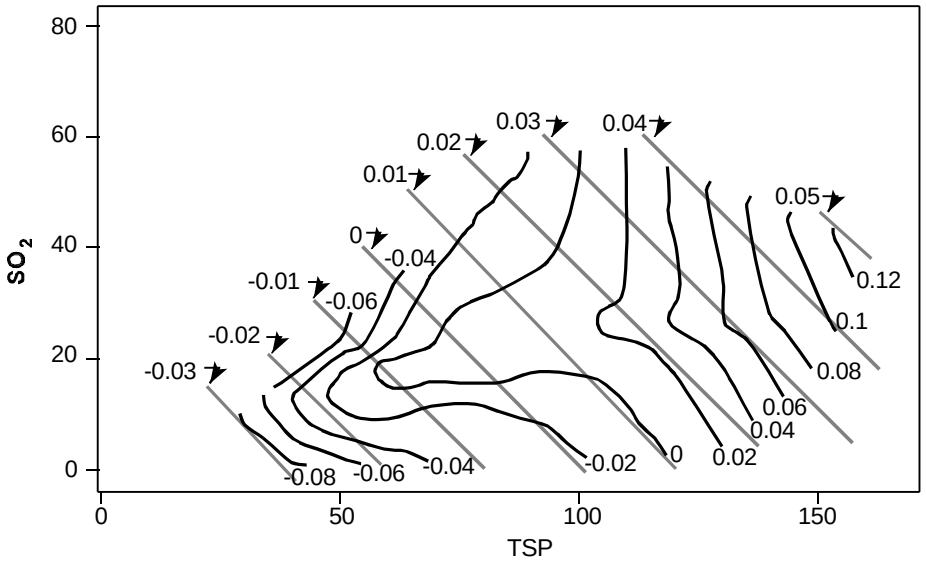

Figure 12-40. Contours depicting the fractional change in Philadelphia mortality in summer by levels of total suspended particles (TSP) and sulfur dioxide (SO_2). Straight line show contours predicted by an additive linear model. Contours predicted by LOESS with 10.2 equivalent degrees of freedom are shown in curved lines.

Source: Adapted from Samet et al. (1995).

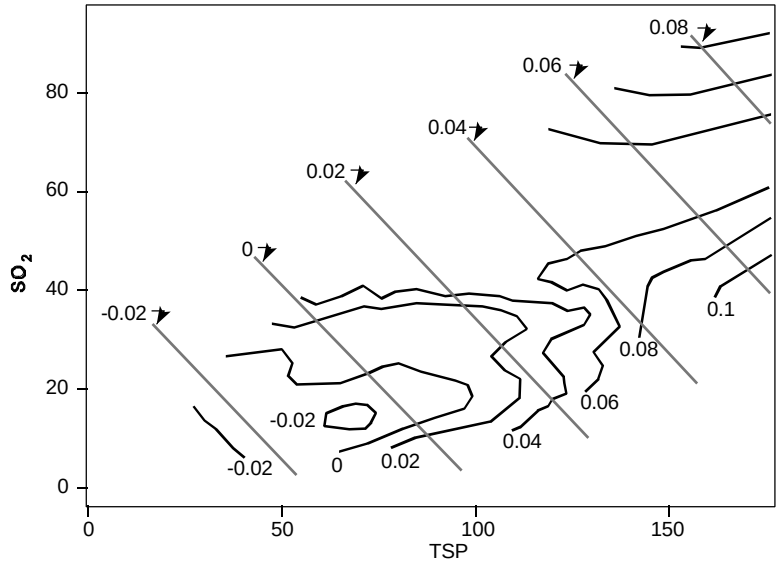

Figure 12-41. Contours depicting the fractional change in Philadelphia mortality in fall by levels of total suspended particles (TSP) and sulfur dioxide (SO_2.) Straight lines show contours predicted by an additive linear model. Contours predicted by LOESS with 10.2 equivalent degrees of freedom are shown in curved lines.

Source: Adapted from Samet et al. (1995).

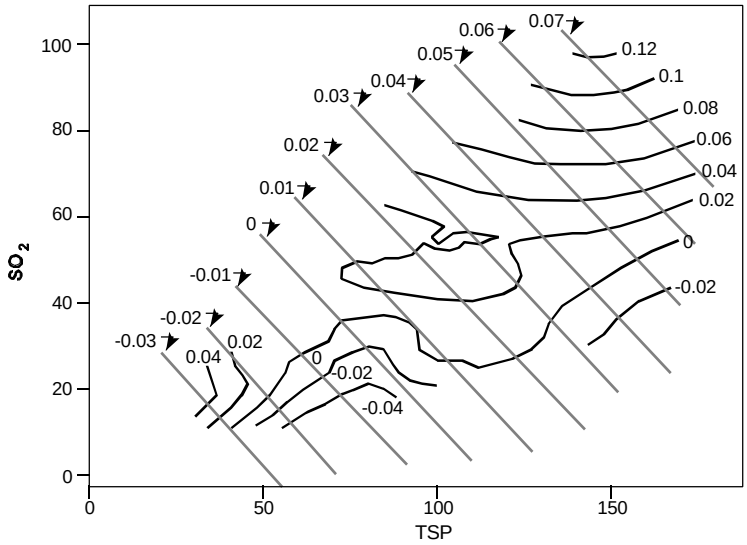

Figure 12-42. Contours depicting the fractional change in Philadelphia mortality in winter by levels of total suspended particles (TSP) and sulfur dioxide (SO_2). Straight lines show contours predicted by an additive linear model. Contours predicted by LOESS with 10.2 equivalent degrees of freedom are shown in curved lines.

Source: Adapted from Samet et al. (1995).

110 $\mu g/m^3$ and SO_2 greater than about 20 ppb, the nonparametric surface contours are roughly parallel to the vertical axis, suggesting a fairly strong dependence of mortality on TSP with little additional effect of SO_2. For TSP less than 110 $\mu g/m^3$, the contours are very complex and suggest a small excess of mortality for SO_2 between 20 and 40 ppb, with results for higher values of SO_2 somewhat uncertain because of the virtual absence of high SO_2 data on days with low TSP.

Fall results are shown in Figure 12-41. For TSP greater than about 100 $\mu g/m^3$ and SO_2 less than about 40 ppb, the nonparametric surface contours are roughly parallel to the vertical axis, suggesting a strong TSP effect in this range. For TSP less than about 100 $\mu g/m^3$, the nonparametric surface contours are roughly parallel to the horizontal axis, showing little effect of TSP in this range.

Winter results are shown in Figure 12-42. For TSP between about 80 and 100 $\mu g/m^3$ and SO_2 less than about 30 ppb, the nonparametric surface contours are roughly parallel to the vertical axis suggesting some TSP effect, but otherwise SO_2 appears to be the dominant pollutant for winter mortality since the contour lines generally parallel the horizontal axis. This can be visualized more effectively using the three-dimensional plot in Figure 12-37. One-dimensional nonparametric models for mortality versus TSP and mortality versus SO_2 are shown in the HEI report (Samet et al., 1995; Figure 11). These figures, based on generalized additive models, suggest a somewhat complex relationship with lower RR for total mortality at TSP less than 90 to 100 $\mu g/m^3$, a sharp increase at higher TSP levels, whereas the relationship of excess mortality to SO_2 is sharply increasing at SO_2 below 20 ppb, flat above 20 ppb. The relationship of mortality to TSP is flat for people less than 65 years of age, but sharply increasing at TSP greater than 50 $\mu g/m^3$ for people age 65 years or greater. Age and other factors affecting the susceptible subpopulation(s) such as weather and copollutant stresses may be contributing factors in the apparent nonlinear and interaction between PM and other variables that was observed in the multidimensional mortality concentration-response surfaces plotted in Figures 12-36 through 12-42.

While these plots may invite some overinterpretation several important points have been established by the nonparametric modelling of concentration-response surfaces for the Philadelphia mortality data:

(1) Both TSP and SO_2 were associated with significant increases in mortality in Philadelphia during 1973-1980, even after adjustments for weather-related effects, but there were important differences in effect depending on season and on the range of TSP or SO_2 values;

(2) There was indication of a relatively large relationship between TSP and excess mortality during spring and summer, for TSP larger than about 100 $\mu g/m^3$; even during these seasons, there was little evidence for a TSP relationship with mortality at substantially smaller TSP concentrations;

(3) There was a relationship between SO_2 and excess mortality at TSP concentrations below 75 $\mu g/m^3$, but the relationship was not evident at SO_2 concentrations above about 50 ppb or TSP concentrations above about 75 to 100 $\mu g/m^3$;

(4) There is little basis for assuming that analogous results would be obtained for other PM indices, such as PM_{10} or $PM_{2.5}$.

In the studies discussed in Sections 12.3 and 12.4, many of the analyses are based on additive linear models for the copollutants. Based on the preceding discussion, there may be some unresolved questions about the adequacy of the fitted models to accurately characterize the joint effects of the PM index and other pollutants. Therefore the estimated RR and statistical significance of PM and other pollutants as predictors of health endpoints may be biased by the misspecification of the joint or multivariate concentration-response surface for the multiple pollutants.

The excess risk contours change orientation between 75 and 125 µg/m^3 TSP. It is clearly not correct to conclude from the additive linear model results that one pollutant is always (or never) a better predictor of excess mortality in Philadelphia than is the other pollutant. Seasonal differences also seem to play an important role.

The Samet et al. analyses suggest that interpretation of the results of fitting additive linear models using two or more pollutants may be premature without considering in some detail the exact nature of the interactions among the pollutants, and possibly also the effects of interactions (i.e., adjustments and effect modifications) involving weather and other covariates. In particular, the conclusion from an additive linear model that inclusion of copollutants generally lowers the effect attributable to PM may not apply to a more accurate nonparametric model. It is possible that for certain ranges of PM concentrations, inclusion of copollutants in the model makes little or no difference for the estimated PM effect, and for some ranges of the copollutants, the estimated

PM effect might even be larger than the overall PM effect estimated from a linear model. These differences or PM effect modifications may vary from city to city or from season to season. There is little basis for generalizing these findings beyond these 8 years of data from one city.

The underlying problem of modeling multiple pollutants is very similar whether the study data are derived from daily time series, from long-term prospective studies, or from population-based studies. In most analyses of population-based data, an additive linear model for the *logarithm* of the pollutant concentration is used, which may not alter the fundamental problem that the additive linear model may still be a misspecification of the relationship.

The conclusion that the RR estimates from fitting a linear model with a single pollutant are upper bounds of that pollutant's RR should not be taken as true in general, for all pollutants and all concentration ranges. Tests of the adequacy of the additive linear model specification have not been reported in general, and it is likely that investigations of other data sets will find more situations in which the standard additive linear model is not adequate for evaluating the health effects of multiple pollutants.

Summary

In summary, confounding by weather and by time effects can be adjusted statistically so as to remove a substantial amount of confounding, but possibly at the expense of reducing the estimated PM effect by attributing it to weather or longer-term time effects not related to short-term PM exposure. Confounding by co-pollutants sometimes cannot be avoided, but should be diagnosed and reported more completely than in most studies now available. In studies where sensitivity analyses demonstrate that including other pollutants in the model causes little change in either the RR estimate for PM or on the width of the confidence interval for the PM effect, one may conclude that the model is not seriously confounded by co-pollutants. Since a number of mortality and morbidity studies have shown that the PM effect on health is not sensitive to other pollutants, we may conclude that the PM effects in these studies are real. This adds some credibility to the claim that a significant PM effect exists in the remaining studies where PM is statistically significant in a model without other pollutants, though similar in magnitude to the PM effect found in other studies with less co-pollutant confounding, but is not statistically significant when other pollutants are included in the model. This then provides a basis for the meta-analyses discussed below.

12.6.3.6 Ecological Study Design

Most of the studies considered are ecologic in design. Even in the daily longitudinal studies, individuals are grouped by region, SMSA, or catchment area for hospital admissions, and all are assumed to have exposure to PM and other covariates characterized by a single numerical value for the area on that day. The "ecological fallacy" refers to the biases inherent in making individual-level predictions from aggregate-level data. However, such studies are often used because of the availability of data bases for air pollution, weather, and mortality or hospital admissions on a daily basis. Relative risk estimates for individuals should therefore be regarded as subject to much uncertainty, even for age-specific sub-populations, in the absence of subject-specific exposure and covariate data. Recent additions to the NCHS mortality data base, including demographic information such as educational attainment, may allow better resolution of the effects of socio-demographic covariates. While residential location might improve estimates of exposure in communities with several monitoring sites, there would still be considerable uncertainty about individual non-residential exposures in the absence of information about daily activity. Better individual exposure information would still be needed to reduce the substantial uncertainties about exposure.

12.6.3.7 Measurement Error

While there has been much discussion about the effects of measurement error, particularly with respect to exposure misclassification, few suggestions have been made as to how to deal with this question.

There have been few quantitative assessments of errors in measurements of particulate matter or other copollutants. There are at least two major components of these errors.

(1) Instrument error: Errors in measurement of pollutant levels at the point of measurement.

(2) Proxy error: Error in using levels at a point (even if correctly measured) as the levels to which study population members are exposed.

For studies of chronic effects, another potentially important problem is sometimes dealt with under the heading of "exposure definition":

(3) Construct error: Error in using a particular exposure summary other than the biologically relevant exposure (for example, using time-weighted average level when only time above a critical threshold is biologically relevant). This is also encountered in constructing moving averages for short-term studies.

It is often assumed that any measurement error is nondifferential, and that consequently any bias produced by the error would be towards the null. Neither assumption is necessarily correct. There are several possible scenarios under which proxy measurement errors will be differential. For example, suppose monitor readings in low-pollution, low-mortality areas tend to understate exposure more than in high-pollution, high mortality areas because many residents of low-mortality areas commute to jobs in high-mortality areas. Then measurement errors will be differentially higher for low-mortality populations (and among noncases in an individual-level study based on these measurements and areas).

Contrary to popular treatments, nondifferential error does not guarantee that the resulting bias in effect estimates is towards the null. In ecologic designs, nondifferential error in individual-level exposure measurements can easily produce very large bias away from the null. In individual-level designs, nondifferential error may produce bias away from the null if errors are interdependent or if the dependence of measured on true levels is not monotonic. Interdependence of errors seem likely. For example, wind patterns would induce correlated proxy errors in all atmospheric pollutants. Effects of confounder errors can be in either direction, whether or not the errors are nondifferential. Under the best of circumstances the only predictable effect of nondifferential confounder errors is that they will tend to leave the exposure effect estimates partially confounded. A recent study by Schwartz et al. (1996) suggests that the effects may be small in daily mortality studies.

In summary, there has been no evidence presented that measurement errors are nondifferential. Even if there were such evidence, it would not imply that the biases produced by the errors are toward the null. Bias due to measurement error can be profound.

12.6.4 Assessment Issues for Epidemiology Studies

12.6.4.1 Significance of Health Effects/Relevancy

The "relative risks" derived from the regression coefficients in recent short-term PM/mortality studies appear to be consistently "small" (i.e., 1.025 to 1.05 per 50 $\mu g/m^3$ increase in PM_{10}), compared (at a face value) to the relative risks in other types of studies. In cancer

epidemiology, for example, some (Shapiro, 1994) consider a relative risk of 1.7 as weak support, "at most", for a causal inference. However, much lower RR estimates of 1.2 to 1.3 have been regarded as sufficient for establishing a presumption of a causal relationship for health effects from environmental pollutants in recent EPA studies on environmental tobacco smoke (U.S. Environmental Protection Agency, 1992) and nitrogen oxides (U.S. Environmental Protection Agency, 1993).

The fact that a relationship is weak, or that an effect is small, does not mean that the relationship is not causal. As Rothman (1986, pp. 17-18) points out, "By 'strength of association', Hill [1965] means the magnitude of the ratio of incidence rates. Hill's argument is essentially that the strong associations are more likely to be causal than weak associations because if they were due to confounding or some other bias, the biasing association would have to be even stronger and would therefore presumably be evident. Weak associations, on the other hand, are more likely to be explained by undetected biases. Nevertheless, the fact that an association is weak does not rule out a causal connection." Many of the studies cited in this chapter included substantial assessments of the effects of potential confounding factors, particularly age group, identifiable cause of death or hospital admission, weather or climate, and the levels of co-pollutants. In some cases, potentially confounding factors were either not present or present at such levels as to have an negligible effect on the health outcome. Even when potential confounders were present, it was often possible to carry out a statistical adjustment for the confounder, with the PM effect size estimated with and without the potential confounder in the model. The PM effect size estimates and their statistical uncertainty in many studies showed little sensitivity to the adjustment for confounding variables. In a few other studies, there was substantial confounding with some co-pollutants such as SO_2 or O_3, but estimates of RR for PM without inclusion of the confounders in the statistical concentration-effect model used in these studies were quantitatively similar to RR estimates from other studies where confounding was either avoided or was shown statistically to have little effect. This bears out the comment by Rothman (1986, p. 18) that "... the strength of an association is not a biologically consistent feature, but rather a characteristic that depends on the relative prevalence of other causes," which here includes confounders such as weather and co-pollutants.

However, these two types of relative risks are not directly comparable. The "relative risk" estimates used in these short-term PM exposure studies are not only "acute" in their

exposure/response relationship, but also represent "indirect" cause of deaths. A healthy person does not develop respiratory disease and die from an exposure to 100 $\mu g/m^3$ PM_{10} in one day. The causal hypothesis is that people with chronic respiratory or cardiovascular diseases, who may be near death from the preexisting conditions, are pushed toward death prematurely by the additional stress on the respiratory system imposed by an increased level of air pollution. This is in contrast to a cancer risk from exposures to a chemical, through which a perfectly healthy person may develop cancer and die at the age of 50, when the person may otherwise have lived up to 70 years old. This difference may be obvious to the researchers analyzing these data, but needs to be clarified when such "risk estimates" are communicated to people who are not familiar with this field. Estimates of life shortening attributable to short-term and chronic PM exposure are not available.

With this difference taken into consideration, there are several reasons why we may be concerned about the estimated "relative risks":

- The apparent "relative risk" estimates are often calculated for the entire death categories. Cause-specific "relative risk" estimates are often greater than for total mortality (e.g., in Pope et al.'s Utah study, the excess relative risk calculated for the respiratory category mortality was 43% as opposed to 16% for total mortality). If susceptible populations were defined and categorized, for example by age, the risk estimate would be even higher than for the general population.

- The apparent "relative risk" tacitly assumes a baseline death population in which all are subject to the change in PM exposures. It is likely that this is not the case. An unknown fraction of the population are not subject to the change in exposure levels of outdoor PM, thereby causing an underestimation of the risk of those actually exposed.

- There may be a downward bias in the estimated PM/mortality regression coefficients (and, therefore, in the estimated relative risk) due to the PM measurement errors. The extent of this bias is not known.

- The extent of prematurity of the deaths, which may range from days to years, is not known.

12.6.4.2 Biological Mechanisms

Most of speculation on the biological mechanism of PM mortality effects were made in the earlier major air pollution episodes. According to Firket's report (1936) on the fog episode of Meuse Valley in 1930, the autopsies with microscopical examinations found local and superficial

irritation of the mucus membrane of the respiratory ducts and the inhalation of fine particles of soot in the pulmonary alveoli. The chemists concluded that "the SO_2 in the presence of oxidation catalysts such as ferric and zinc oxide, must have been partly transformed to sulfuric acid". The discussion of the report suggested sulfuric acid to be "the most probable cause" of deaths. In the 1952 London fog episode (United Kingdom Ministry of Health, 1954), the association of the air pollution and the observed increase in deaths, estimated to be 4,000 excess deaths, was rather obvious. The report suggested "it is probable that sulphur trioxide dissolved as sulphuric acid in fog droplets, appreciably reinforced the harmful effects of sulphur dioxide." One immediate cause of death was speculated to be acute anoxia from bronchospasm.

Health effects observed at current air pollution levels are more subtle, as in recent PM/mortality studies. There are some speculations regarding possible mechanisms, identifying specific chemical components responsible for the effects such as acid aerosols. The pattern that does appear to resemble the past episodes in these more recent observational studies is the age and cause specificity of the deaths associated with PM. Both cardiovascular and respiratory deaths in the elderly population increased in the 1952 London episode. The estimated relative risks for these categories were found to be disproportionately higher and more significant in the analysis of Philadelphia (Schwartz, 1994b,c). Other cause specific analyses (e.g., Fairley, 1990; Pope et al., 1992; Schwartz, 1994b) also reported higher estimated relative risks for respiratory and cardiovascular categories than total or other categories. While the excess deaths in the cardiovascular category, which was also apparent in past episodes, do not provide direct information on possible causal mechanisms, the analysis of contributing causes (Schwartz, 1994h) appears to suggest that the respiratory illness is contributing to the deaths of people with cardiovascular conditions. If a person has been suffering from a major cardiovascular disease, that person's death may be still categorized as cardiovascular, even if the respiratory condition causes the death. Such misclassification may also occur for other categories (e.g., cancer). More analyses using the contributing cause of deaths are needed to further characterize such mechanisms.

12.6.4.3 Coherence

Factors involved in evaluating both the data and the entire group of epidemiological studies, include the strength of association, the consistence of the association, as evidenced by its repeated observation by different persons, in different places, circumstances and time, and the coherence with other known facts (Bates, 1992). One can look for interrelationships between different health indices to provide a stronger and more consistent synthesis of available information. The various findings that support a picture of coherence would provide a stronger case with quantitative studies as opposed to qualitative studies. Other studies may be inappropriate to use in such a discussion, the quality of the study should be considered. Bates (1992) states that the difficulty with discussing any index of internal coherence is that this requires a series of judgements on the reliability of the individual findings and observations. The outcome of a coherence discussion then is a qualitative presentation.

Bates (1992) also noted that the strength of different health indexes are important as are difficulties in assessing exposure. Bates (1992) also suggests three areas to look for coherence: (1) within epidemiological data, (2) between epidemiological and animal toxicological data, and (3) between epidemiological, controlled human and animal data.

Coherence by its nature considers biological relationships of exposure to health outcome. The biologic mechanism underlying an acute pulmonary function test reduction in children is most likely not part of the acute basis for a change in the mortality rate of a population exposed in an older group of individuals. In looking for coherence one can compare outcomes that look at similar time frames—daily hospitalizations compared to daily mortality or acute versus chronic outcomes. Overall the data indicates that PM has a relationship with a continuum of health outcomes, but the underlying mechanisms may be different.

Coherence in the overall data base can be considered within the endpoint and/or in other endpoints. The principal health outcome for which coherence is desirable is mortality, the death rate in a population. Of the various morbidity outcomes studied and discussed in the earlier part of the chapter, hospitalization studies reviewed in the chapter support this notion. The mortality studies suggest that these specific causes provide stronger relationships (i.e., larger RR estimates) than total mortality. The outcome potentially most related is hospital admission for respiratory or cardiovascular causes in the older age group (i.e., > 65 years old). In a qualitative sense, the increased mortality found in that age group are paralled by increased hospital admissions.

Partial coherence is supported by those studies in which increased incidence of different health outcomes associated with PM are found in elderly populations in different cities, as is the case for the following examples, based on currently published studies:

- Detroit: Mortality mainly in elderly populations, hospital admissions for respiratory causes and for cardiovascular causes in the elderly;
- Birmingham: Mortality mainly in the elderly, hospital admissions for the elderly;
- Philadelphia: Mortality and hospital admissions for pneumonia in the elderly;

In the Utah Valley, several studies have been conducted. Mortality and hospital admissions for respiratory causes in adults have been associated with PM in the Utah Valley. Also, pulmonary function, respiratory symptoms, and medication use in asthmatic subjects of all ages; hospital admissions for respiratory symptoms, pulmonary function, respiratory symptoms, and medication use in healthy school children, pulmonary function in symptomatic and asymptomatic children; and elementary school absences in children were found to be associatied with PM exposures in Utah Valley. Another study found a PM effect on pulmonary function in smokers with COPD in Salt Lake Valley. The Utah Valley population was largely non-smoking, so smoking was not likely to be a source of confounding.

While these multiple outcomes did not occur in strictly identical subgroups of each population, there was probably a sufficient degree of overlap to indicate that PM was a significant predictor of a wide range of health outcomes within a specific community. The symptoms serious enough to warrant hospitalization and the major part of the excess mortality occurred in the elderly sub-group of the population. However, a significant decrement in pulmonary function and increased incidence of symptoms associated with daily increases in PM occurred in children in Utah Valley, along with a "quality of life" effect measured by lost school days. Thus, there is evidence for increased risk of health effects related to PM exposure ranging in seriousness from asymptomatic pulmonary function decrements, to respiratory symptoms and cardiopulmonary symptoms sufficiently serious to warrant hospitalization, and to excess mortality from respiratory and cardiovascular causes, especially in those older than 65 years of age.

Children may also be at increased risk of pulmonary function changes and increased incidence of symptoms associated with PM exposure. While we have arrayed these health outcomes in order of increasing severity, there is as yet little indication that there is a progression

of effects in any single individual associated with increasing exposure to PM. The "exposure-response" relationship that is derived in most studies must be understood as characterizing population risk from population exposure. Additional studies are needed to define the relationship(s) among individual exposure to PM and other stress factors, individual risk, and individual progression among disease states. Differences in PM dosimetry in the developing, aged, or diseased respiratory tract may also contribute to increased susceptability.

12.6.5 Meta-Analyses and Other Methods for Synthesis of Studies

12.6.5.1 Background

Several reports have appeared in which results from different studies have been combined, formally or informally, to present an overall effect size estimate for acute health effects. For example, a synthesis of daily mortality studies for seven cities was published by Schwartz (1992a). The seven cities included four TSP studies (Steubenville, Philadelphia, Detroit, Minneapolis) and three PM_{10} studies (St. Louis, Eastern Tennessee, Utah Valley). The daily mortality studies were further analyzed by Schwartz in a later paper (1994b), which added studies from New York, from Birmingham, Alabama, later London studies (1959 to 1972), and a study in Athens, Greece. The RR estimates were combined in formal quantitative meta-analyses, using either unweighted RR estimates, or using a smaller set of estimates weighted by inverse of the estimation variance of the RR coefficient from studies in which the standard error was reported. Several methods were used, and several subsets of the data were tested according as to whether or not the study city was "warm" or the TSP coefficient was adjusted for copollutants.

A recent paper by Dockery and Pope (1994b) extends the research synthesis to a variety of health outcomes, including hospital admissions studies and respiratory function tests. This paper is also based on conversion of different PM measures to an equivalent PM_{10} by applying a scaling factor: 1.0 for PM_{15} and BS, 0.55 for TSP, 4 for sulfates (SO_4), 1/0.60 for $PM_{2.5}$, and 1/0.55 for COH. This synthesis paper uses eight cities for total mortality, four cities for respiratory mortality and for cardiovascular mortality, three cities for hospital admissions for respiratory symptoms, four studies for asthma admissions, and combines three cities with different reasons for emergency room visits. The paper examines the effects of PM on exacerbation of asthma by combining results of two cities for bronchodilator use, and combining three studies for asthmatic attacks. Pulmonary function tests are synthesized from four studies for Forced Expired Volume (FEV_1 and

$FEV_{0.75}$), and six studies for Peak Expiratory Flow (PEF daily, weekly, or longer). Respiratory symptom results are divided into combining six studies reporting lower respiratory symptom results, upper respiratory symptom results, and six studies reporting cough symptom results. The authors conclude that these results demonstrate a coherence of effects across a range of related health outcomes, and a consistency of effects across independent studies by different investigators in different settings.

The synthesis of the epidemiologic evidence in this document presents some unusual problems. Many of the studies showing mortality and morbidity effects are based on relatively small increases estimated with great precision resulting from sophisticated analyses of long series of infrequent events. As a result, relative risks (or odds ratios) of 1.06 are common and often statistically significant. A value of 1.06 would indicate that mortality (or morbidity) is increased by 6% when PM_{10} is increased a specified amount (usually 50 $\mu g/m^3$). Traditionally, relative risks less than 1.5 were considered to be of questionable biological meaning. Although relative risks near 1.06 are not large in magnitude, they may represent a large net effect because the events are so common. The question remains: are these effects real or are they an artifact of the analysis?

A careful review of the analysis techniques in Section 12.6.3 suggests that similar results are obtained as long as similar covariates and independent variables are included in the analysis. There are remaining questions about the accuracy of the variances and the assumptions upon which they are based. Even allowing for these problems, the estimated regression coefficients are consistently estimating the correct quantities although the exact p-values may be slightly in error.

The results do not appear to depend heavily on the form in which covariates were included in the model. Analyses that included the known covariates such as temperature and season usually gave similar results. The one factor which appeared to make a consistent difference was the inclusion of one or more copollutant(s) in addition to particulate matter. The inclusion of SO_2 tend to reduce the effect of particulate matter in most analyses, while O_3 generally had less of an impact on PM regression coefficients. This would be expected because O_3 tends to be less correlated with PM than does SO_2. Although the PM coefficients were reduced by the inclusion of SO_2, most remained statistically significant.

One unresolved question is the possibility that the effects seen were the result of some covariate which, had it been included, would have reduced the PM coefficients to a non-significant level. Although this is always a concern with epidemiologic studies, the concern is

often dismissed as improbable when the relative risks are large as 1.5 or 2.0. When the relative risks are less than 1.1, the question is of greater concern.

12.6.5.2 Meta-Analyses Using Studies Reviewed in This Document

In order to compare the results of the various studies relating acute exposure to PM to excess mortality, we selected studies that satisfied certain criteria: (1) the study has been published or is in press; (2) the study used PM_{10} or TSP as an index of particulate matter exposure; and (3) the study included adequate adjustments for seasonality, weather, other effects. The first criterion was imposed to provide adequate access to a description of study data, methods, and results; and the second so as to restrict consideration to studies with pollutants for which EPA has extensive air monitoring data. Even here, analyses were performed separately for PM_{10} studies and for TSP studies, so as to avoid having to make any assumptions about site-specific calibrations of one PM concentration or index into another. It may be possible to extend the meta-analyses to a wider range of studies when methods are developed for assessing the uncertainty associated with generic versus city-specific calibrations of one PM index to another.

The results of the analyses have been standardized for purposes of comparison. All of the acute exposure studies used Poisson or equivalent regression methods with the expected mortality an exponential function of a linear combination of predictors, or with the logarithm of the mortality rate as a linear combination of predictors including the PM index. This means that the relative risk (RR) -- the fractional increase in the mortality rate relative to a baseline value without pollution, everything else being equal -- can be expressed in terms of changes per unit of pollution. The base unit for change in risk was chosen differently for each pollutant. For PM_{10} studies, the effect was the odds ratio for mortality corresponding to an increase of 50 $\mu g/m^3$ in PM_{10}. Other ranges have been used in published papers, most commonly 10 or 100 $\mu g/m^3$. We selected 50 $\mu g/m^3$ because it is closer to the range of values in various morbidity studies, whereas the range in mortality studies usually is larger than 100 $\mu g/m^3$. Since the range of values in TSP studies is typically much larger than in PM_{10} studies, we used 100 $\mu g/m^3$ as the base unit for TSP studies of mortality.

The basic data on effects size estimates, in appropriate units, are shown earlier in Tables 12-2 and 12-4. Note that the confidence intervals derived in the various papers are not

always symmetric about the estimated RR. The data could be naturally sorted into six distinct groups:

- Estimates of PM_{10} effect on RR, not adjusted for copollutants, lags <2 d (4 studies, 4 cities)
- Estimates of PM_{10} effect on RR, not adjusted for copollutants, lags >2 d (6 studies, 6 cities)
- Estimates of TSP effect on RR, not adjusted for copollutants (4 studies, 3 cities)
- Estimates of PM_{10} effect on RR, adjusted for copollutants (3 studies, 3 cities)
- Estimates of TSP effect on RR, adjusted for SO_2 (3 studies, 2 cities)
- Estimates of PM_{10} effects on RR short, long lags (3 studies, 3 cities)

There are presently no methods for using results of different analyses of the same data set, such as the two studies on Steubenville (Schwartz and Dockery, 1992b; Moolgavkar et al., 1995a). (For this assessment, we report results using each separately.)

The meta-analysis methods were similar to those used in the nitrogen oxides criteria document (U.S. Environmental Protection Agency, 1993; Hasselblad et al., 1992). Differences among studies are regarded as random effects. The U.S. EPA meta-analyses results are shown in Figures 12-43 through 12-48 and Table 12-33. The relative risk for

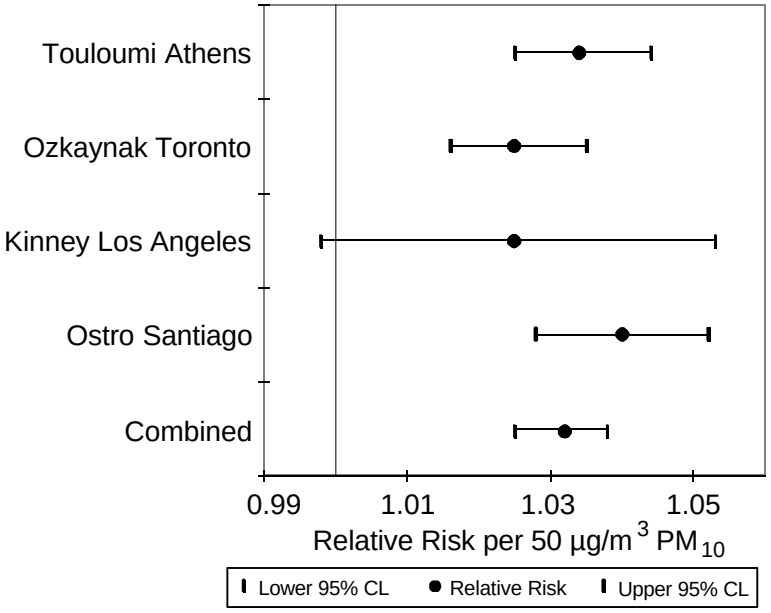

Figure 12-43. Summary of studies used in a combined U.S. Environmental Protection Agency meta-analysis of PM_{10} effect on mortality with short averaging times (0 to 1 day), and co-pollutants in the model.

Source: Touloumi et al. (1994); Ozkaynik et al. (1994); Kinney et al. (1995), and Ostro et al. (1996).

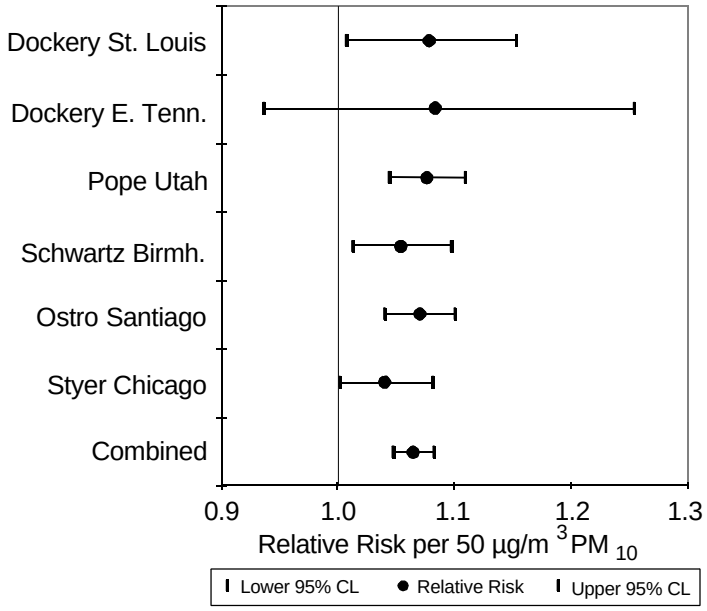

Figure 12-44. Summary of studies used in a combined U.S. Environmental Protection Agency meta-analysis of PM_{10} effects on mortality with longer averaging times (3 to 5 days), and no co-pollutants in the model.

Source: Dockery et al. (1992); Pope et al. (1992); Schwartz et al. (1993a); Ostro et al. (1995b); and Styer et al. (1995).

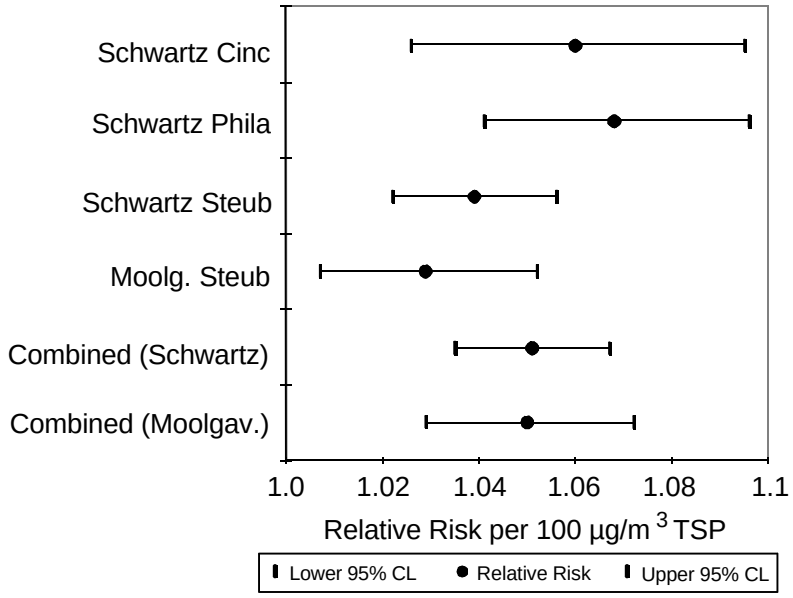

Figure 12-45. Summary of studies used in a combined U.S. Environmental Protection Agency meta-analysis of total suspended particles (TSP) effects on mortality, with no co-pollutants in the model.

Source: Schwartz (1994a); Schwartz and Dockery (1992a); Schwartz and Dockery (1992b); Moolgarvkar et al. (1995a).

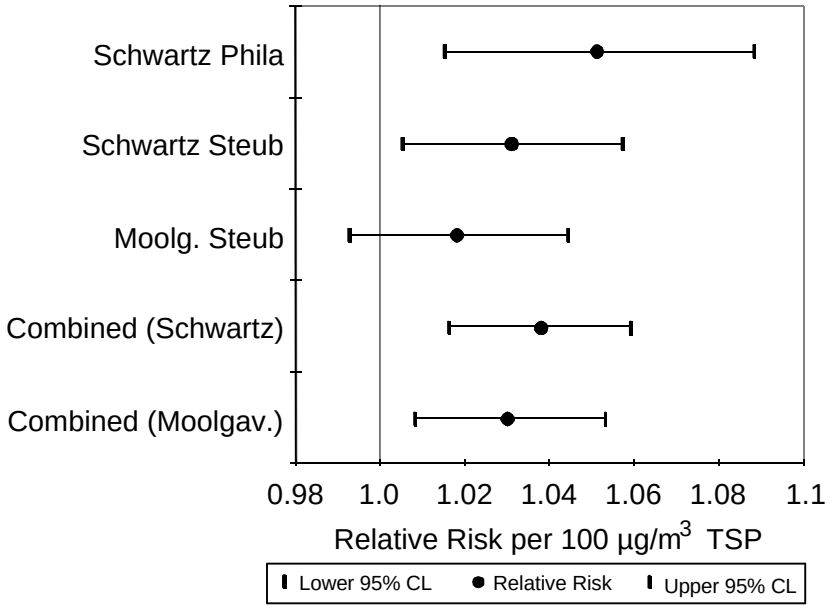

Figure 12-46. Summary of studies used in combined U.S. Environmental Protection Agency meta-analysis of total suspended particles (TSP) effects on mortality, with sulfur dioxide in the model.

Source: Schwartz and Dockery (1992a); Schwartz and Dockery (1992b); Moolgarvkar et al. (1995a).

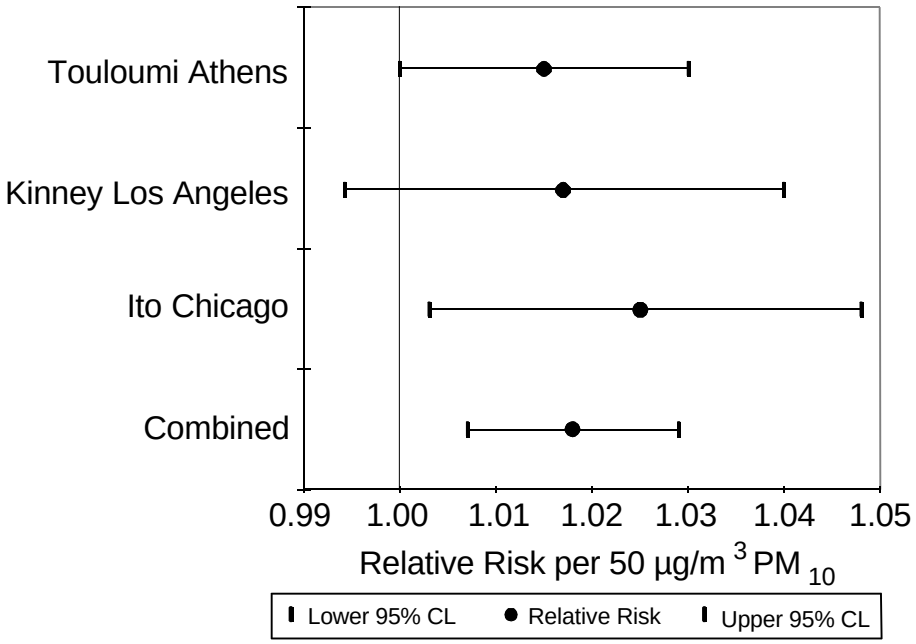

Figure 12-47. Summary of studies used in a combined EPA meta-analysis of PM_{10} effects on mortality, with other pollutants in the model.

Source: Touloumi et al. (1994); Kinney et al. (1995); Ito et al. (1995).

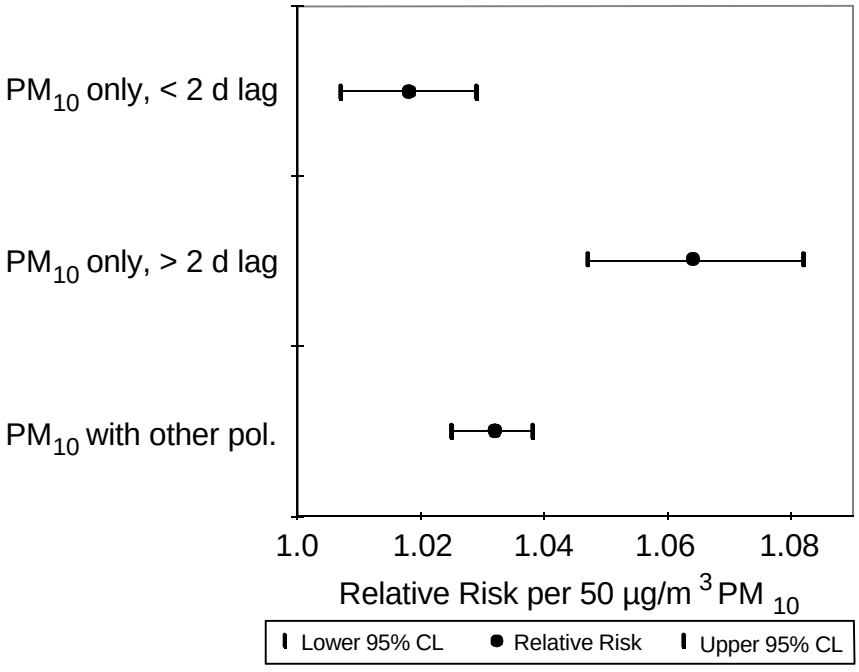

Figure 12-48. Summary of PM_{10} effects on mortality.

Source: U.S. Environmental Protection Agency meta-analyses.

PM_{10} exposure averaged $\leq$2 days is estimated as 1.031 per 50 $\mu g/m^3$ PM_{10}, with a 95% confidence interval of 1.025 to 1.038 per 50 $\mu g/m^3$ PM_{10}. There is overall evidence of an effect, even though one of the four studies in Figure 12-43 is not significant. The relative risk for PM_{10} exposure with longer averaging times, 3 to 5 d, is estimated as 1.064 with 95% confidence interval of 1.047 to 1.082. In Figure 12-44, one study is negative and another marginally significant. The combined estimate for TSP effect in Figure 12-45 depends on which study is used for the Steubenville estimate; with the Schwartz study, the effect is 1.051 per 100 $\mu g/m^3$ TSP, whereas with the Moolgavkar study, the estimate is 1.050, but is less certain. However, none of these studies included SO_2, the most probable confounding co-pollutant. The analogous estimates for a TSP effect with copollutants in the model is less significant across three studies, as shown in Figure 12-46. Also, Figure 12-47 shows that when SO_2 is included in the model, estimated PM_{10} effects still remain significant. RR = 1.018 with a 95% confidence interval from 1.007 to 1.029 per 50 $\mu g/m^3$ PM_{10}. The overall EPA meta-analyses results are summarized in Table 12-37 and Figure 12-48.

TABLE 12-37. U.S. EPA META-ANALYSES: COMBINED ESTIMATES OF RELATIVE RISK OF INCREASED MORTALITY FROM ACUTE EXPOSURE TO AIR POLLUTANTS

Pollutant	Increment	Model	Averaging Time	Relative Risk Estimate Per Increment	95 Percent Confidence Limits
PM_{10}	50 $\mu g/m^3$	No copollutant	0-1 days	1.031	1.025 to 1.038
PM_{10}	50 $\mu g/m^3$	No copollutant	3-5 days	1.064	1.047 to 1.082
TSP	100 $\mu g/m^3$	No SO_2		1.051[1]	1.035 to 1.067
TSP	100 $\mu g/m^3$	No SO_2		1.050[2]	1.029 to 1.072
PM_{10}	50 $\mu g/m^3$	+copollutants		1.018	1.007 to 1.029
TSP	100 $\mu g/m^3$	+SO_2		1.038	1.016 to 1.059
TSP	100 $\mu g/m^3$	+SO_2		1.030	1.008 to 1.053

[1]Including Schwartz Steubenville study.
[2]Including Moolgavkar Steubenville study.

We conclude that there is a short-term increase in mortality in response to acute PM exposures. This appears to be at least partly confounded with other pollutants, especially SO_2,

but even with SO_2 included in the model the effect is on the order of 1 to 5% increase in relative risk per 100 $\mu g/m^3$ TSP. This is probably a minimum estimate of effect size. If SO_2 is in fact a proxy for fine particle exposure through the SO_2 to sulfate to fine particle pathway, then adjusting for SO_2 may overcontrol the estimate of PM effect, which could be as large as 1 to 5% per 100 $\mu g/m^3$ TSP, or 2 to 6% per 50 $\mu g/m^3$ PM_{10}. This also depends on PM_{10} averaging times, with a 3% increase for averages of current and preceding day PM_{10} and 6% effect for 3 to 5 day moving averages.

These analyses suggest that there is an identifiable effect of PM exposure on increases in acute mortality, even when characterized by TSP, a relatively insensitive index of thoracic particle concentration. The role of SO_2 as a possible proxy for fine particle exposure remains to be clarified. It is also not possible to overlook the potential confounding effects of other pollutants such as O_3 and NO_2.

12.6.5.3 Synthesis of Prospective Cohort Mortality Studies

The results of the prospective cohort mortality studies are shown in Table 12-16. The California nonsmoker study is not readily compared quantitatively to the other two studies and so will not be used in a quantitative synthesis. The ACS and Six City studies have many points of similarity, as demonstrated in Table 12-38. Two kinds of relative risk comparison are shown for all causes of death, for death by lung cancer and by cardiopulmonary causes, and for all other internal and external causes. The first comparison between the ACS and Six City studies is the relative risk of smoking for current smokers compared to never-smokers. Even though these two studies were completely independent, covering different populations with different recruitment strategies, the general and disease-specific risk rates of smoking for the two studies are strikingly similar, suggesting that other results from the studies may be sensibly compared or combined. The last three columns in Table 12-38 compare the risk rates of the least polluted and most polluted cities in the respective studies. There are two comparisons for the ACS study, based on 151 cities with sulfate data and 50 cities with fine particle data, and 6 cities in the other study. Steubenville OH was the most polluted comparison city in the ACS sulfate and Six City comparison, and the community of

TABLE 12-38. ADJUSTED MORTALITY RISK RATIOS FOR SMOKING AND FOR PARTICULATE MATTER EXPOSURE BY CAUSES OF DEATH IN TWO RECENT PROSPECTIVE COHORT STUDIES

	Current Smokers Versus Non-smokers		Most Versus Least Polluted City [1]		
			ACS		6-City
Cause of Death	ACS	6-City	Sulfate	$PM_{2.5}$	----
All Causes	2.07 (1.75, 2.43)	2.00 (1.51, 2.65)	1.15 (1.09, 1.22)	1.17 (1.09, 1.26)	1.26 (1.08, 1.47)
Lung Cancer	9.73 (5.96, 15.9)	8.00 (2.97, 21.6)	1.36 (1.11, 1.66)	1.03 (0.50, 1.33)	1.37 (0.81, 2.31)
Cardio-pulmonary	2.28 (1.79, 2.91)	2.30 (1.56, 3.41)	1.26 (1.16, 1.37)	1.31 (1.17, 1.46)	1.37 (1.11, 1.68)
All other	1.54 (1.19, 1.99)	1.46 (0.89, 2.39)	1.01 (0.92, 1.11)	1.07 (0.92, 1.24)	1.01 (0.79, 1.30)

[1]ACS sulfates, 151 cities (Great Falls, MT versus Steubenville, OH); ACS fine particles, 50 cities, (Albuquerque, NM versus Huntington, WV); Six City study (Portage, WI versus Steubenville, OH).

Huntington, WV (also in Ohio River valley) the most polluted community in the fine particle comparison. The RR for 25 $\mu g/m^3$ $PM_{2.5}$ is 1.17 (1.09, to 1.26) in the ACS study and 1.31 (1.11 to 1.68) in the Six-City Study. The RR for 15 $\mu g/m^3$ sulfate is 1.10 (1.06 to 1.16) in the ACS study and 1.46 (1.16 to 2.16) in the Six City Study. The average for the two studies (random effects weighting) is RR = 1.18 (1.04, 1.33) for 25 $\mu g/m^3$ $PM_{2.5}$ and RR = 1.11 (0.90 to 1.36) for 15 $\mu g/m^3$ sulfate.

12.6.5.4 Discussion

In general, there appears to be a range of acute health responses to air pollution exposure as characterized by some PM indicator. Dockery and Pope (1994b) have stated that "It is ... presumptuous to assign these adverse health effects solely to the mass concentration of particulates. ... Many health effects of particles are thought to reflect the combined action of the diverse components of the pollutant mix." Since pollutant mixes and exposed populations differ from one location to another, it is more probable that there are real differences among different studies.

Several approaches to estimating a combined PM effect as a weighted average of study-specific effects may be considered: (1) regard each effect size estimate as a measurement in an ecological study and adjust for differences in effect size among cities as a function of differences in climate, mixture of other air pollutants, and differences in demographic characteristics; (2) carry out multiple comparisons of effect size estimates and group together those estimates that are not significantly different; (3) perform combined analyses in which the PM effect size parameter(s) are constrained to be equal in different data sets.

With the first approach (1), it may be possible to model the differences in PM effect size estimates by multiple regression on known quantitative differences in climate, copollutant mix, and population. This would require a "meta-regression" in which some assumptions would need to be made about the relationship between PM effect size and the inter-study variables that distinguish different cities, adding yet another layer of uncertainty about model specification. It would not be feasible to carry out this analysis unless there were a large enough number of studies, since multiple linear regression models do not perform well unless there are several times as many data values (effect size estimates from different studies) as there are variables that are used for adjustment.

With approach (2), each effect size estimate for which there was an attached standard error estimate would be compared with each other effect size estimate, as if each effect size estimate was a separate group mean in an analysis of variance. The effect size estimates would then be grouped into clusters in which the cluster members (studies) were not statistically different from each other, although some methods allow for the possibility of partially overlapping clusters. A variety of multiple comparison procedures are available, using either methods based on normally distributed data or more robust methods (e.g., Hochberg and Tamhane, 1987). Some comparisons of a multiple hypothesis testing approach with a metaanalysis approach are described by Westfall and Young (1993), who prefer computer-intensive resampling methods such as bootstrap estimation or permutation testing that may not be feasible unless raw data were available. Conventional multiple testing methods can be done without raw data when standard error estimates are available, and may be especially suitable when there are only a few effect size estimates.

With alternative approach (3), it is essential that raw data be available. It is unlikely that raw data for all studies of any specified health outcome could be assembled within a short period of time, and even then it would likely take months to conduct such an analysis adequately.

The formal meta-analytic methods used to combine effect size estimates for acute mortality (Schwartz, 1994c) or for a variety of health outcomes (Dockery and Pope, 1994b) could possibly be improved by including more information when weighing the studies, as suggested above. There are still many unresolved questions about how the synthesis of PM health effects data from different studies should be carried out.

12.7 SUMMARY AND CONCLUSIONS

Several uncertainties need to be considered in interpreting the PM epidemiology studies individually and as a group. Measurement error in exposure is potentially one of the most important methodological problems, and potential confounding due to weather, copollutants and other factors also needs to be considered. Important potential covariates should be adequately controlled, and the response variable should vary as a function of increasing PM exposure. In addition, quantitative studies must estimate PM exposure with reasonable accuracy as a continuous variable. While individual PM studies may not fully take into account the above uncertainties and considerations, as a group, especially within one study type (i.e., acute mortality), PM studies present a relatively consistent picture. Their use in establishing concentration-response parameters, however, still argues for caution in interpreting these studies because no biological mechanism is known for the increases in mortality related to low level ambient PM exposure.

12.7.1 Mortality Effects of Particulate Matter Exposure

The time-series mortality studies reviewed in this and past PM criteria documents provide strong evidence that ambient air pollution is associated with increases in daily human mortality. Recent studies provide confirmation that such effects occur at routine ambient levels, extending to 24 h concentrations below 150 $\mu g/m^3$ (the level of the present U.S. air quality standards). Furthermore, these new PM studies are consistent with the hypothesis that PM is the air pollutant

class most closely associated with the mortality impacts of air pollution. One of the more important findings is that longer averaging times (3 to 5 day moving averages) predict larger and more significant effects on total, respiratory, or cardiovascular mortality in many studies than do PM concentrations on the same or preceding day. Overall as noted in Table 12-4, the PM_{10} relative risk estimates derived from the recent PM_{10} total mortality studies suggest a 24-h average 50 $\mu g/m^3$ PM_{10} increase in acute exposure has an effect on the order of RR = 1.025 to 1.05 in the general population. Higher relative risks are indicated for the elderly and for those with pre-existing respiratory conditions, both of which represent sub-populations at special risk for mortality implications of acute exposures to air pollution, including PM. Results are very similar over a range of specifications of statistical models used in the analyses, and are not artifacts of the methods by which the data were analyzed.

A growing body of evidence suggests that fine particles ($PM_{2.5}$) are most strongly related to excess mortality in both acute and chronic studies. However, while coarse inhalable particles are less strongly implicated in excess mortality, there appears to be some situations in which they may also be predictive of excess mortality.

Evidence for or against threshold effects or other nonlinearities in response is as of yet equivocal. Statistical significance tests for piecewise linear models with a range of cut points (possible thresholds) for effects of TSP on mortality in Philadelphia (Cifuentes and Lave, 1996) show some indication of a nonlinear relationship, with a generally flatter linear relationship between mortality and TSP below the cutpoint than above the cutpoint. However, both linear segments have statistically significant positive regression coefficients at cutpoints around 90 $\mu g/m^3$ TSP, even when other pollutants (SO_2, O_3) are included in the model and the TSP regression coefficients do not appear to be significantly different between the two segments, suggesting that there may not be a threshold for effect. Other analyses of Philadelphia daily mortality series (Samet et al., 1995) suggest that the relationship is moderately nonlinear and nonadditive, but do not provide evidence for either a TSP threshold or a SO_2 threshold. There is strong evidence that the relationships vary by season, however. The Philadelphia results may reflect seasonal or daily changes in the composition and size distribution of TSP. Other acute studies suggest that the relationship between mortality or hospital admissions and PM_{10} do not differ significantly from a linear relationship. On the other hand, some long-term mortality studies suggest a possible threshold for TSP or sulfates. However, because of possible exposure

measurement errors and limited numbers of quantile observations available in piecewise analyses, the detection of a threshold or strongly nonlinear concentration-response relationships may be essentially impossible even if such a relationship actually exists.

There is an indication among these various analyses that children may be more susceptible to the mortality effects of air pollution exposure than the population in general, but it is difficult, given the limited and somewhat conflicting results available at this time, to ascribe any such association to PM pollution in particular. This is an area where further research is clearly needed to broaden the base upon which to assess the potential for PM to increase mortality among children.

Long-term exposure to air pollution was studied by use of cross-sectional studies, comparing rates of mortality or morbidity at a point in time against differences in annual average pollutant concentrations. Most older mortality studies were population-based cross-section studies. These studies used outcome rates for entire cities or SMSA's. Several recent prospective cohort-based cross-sectional studies allow use of subject-specific information about other health risk factors, such as cigarette smoking or occupational exposure; and subject-specific outcome measures. The relative risk estimates show some sensitivity to model specification. For models of 1980 mortality from all natural causes, the RR from separate OLS regression models using TSP, PM_{15}, $PM_{2.5}$ or SO_4 as PM indicators all showed a positive but statistically, non-significant effect. The PM_{15} RR is 1.036 at $PM_{15} = 50\ \mu g/m^3$ (95% confidence interval 0.98 to 1.10), whereas a log-linear model for the same 62 SMSA's found a larger and statistically significant RR for TSP of 1.066 (95% confidence interval 1.006 to 1.13 at TSP = 100 $\mu g/m^3$). The relative risk of major cardiovascular disease (CVD) for sulfate particles was 1.19 at $SO_4 = 15\ \mu g/m_3$ (interval 1.03 to 1.35) when adjusted for one set of demographic covariates, but smaller and not significant after adjustment with a larger set of covariates. The relative risk of COPD for TSP at TSP = 100 $\mu g/m^3$ or for non-sulfur TSP was highly significant, 1.50 and 1.43 with confidence intervals (1.22, 1.83) and (1.20, 1.71), respectively.

Although most of these studies covered the entire U.S. using the basic paradigm of Lave and Seskin (1970), there are major differences in the numbers of independent variables considered, including the air pollutants. Most of the studies found pollutant elasticities (i.e., mean effects) of 0.02 to 0.08, although the specific pollutants associated with mortality varied. However, all of these studies found at least some association between air pollution and mortality

on an annual average basis. There was a slight suggestion that elasticities may be decreasing over time (1960 to 1980). It was not possible to determine whether the mortality associations were stronger for pollution measured the same year or in previous years. Analyses by age and cause of death were limited; the most consistent associations found by Lipfert (1994a) were for the elderly, especially ages 75+, and for respiratory disease mortality and TSP.

Two older and three newer prospective cohort studies of mortality associated with chronic PM exposures were also evaluated. Table 12-16 summarizes the three newer prospective studies considered. The two early studies not shown in Table 12-16 were largely inconclusive, and the studies of California nonsmokers by Abbey et al. (1991a, 1995a,b,c) found no significant mortality effects of previous air pollution exposure. That study, however, and the Six-City chronic mortality study, suffer from small sample sizes and inadequate degrees of freedom, which partially offset the specificity gained by considering individuals instead of population groups. The Six Cities and ACS studies agree in their findings of strong associations between fine particles and excess mortality, but it is unfortunate that the ACS study did not consider a wider range of pollutants so as to also evaluate the extent to which other air pollutants may have contributed to the reported PM effects.

The RR estimates for total mortality are large and highly significant in the Six-Cities study. With their 95 percent confidence intervals, the RR for 50 $\mu g/m^3$ PM_{15} is 1.42 (1.16, 2.01), the RR for 25 $\mu g/m^3$ $PM_{2.5}$ is 1.31 (1.11, 1.68), and the RR for 15 $\mu g/m^3$ SO_4 is 1.46 (1.16, 2.16). The estimates for total mortality in the ACS study are much smaller, but also much more precise, 1.17 for 25 $\mu g/m^3$ $PM_{2.5}$ (RR 1.09, 1.26), and 1.10 for 15 $\mu g/m^3$ SO_4 (RR 1.06, 1.16). Both studies used Cox regression models and were adjusted for rather similar sets of individual covariates. In each case, however, caution must be applied in use of the stated quantitative risk estimates, given that the life-long cumulative exposures of the study cohorts (especially in the dirtiest cities) included distinctly higher past PM exposures than those indexed by the more current PM measurements used to estimate the chronic PM exposures of the study cohorts. Thus, lower risk estimates than the published ones are apt to apply.

An additional line of evidence concerning long-term effects may be seen in comparing some specific causes of death in the prospective cohort studies. Table 12-38 shows relative risk for total mortality, lung cancer deaths, cardiopulmonary deaths, and other deaths in the Six City Study and the ACS study. The RR for current smokers in these two independent studies is very

similar, with no significant differences. The RR for most and least polluted cities in the two studies is the same for total, cardiopulmonary, and other causes of mortality, and the same for lung cancer for sulfates in the ACS study and the Six City study, but not for $PM_{2.5}$ in the ACS study. It is interesting that Abbey et al. (1991a) found a statistically significant relationship between female cancer and TSP in the AHSMOG study, although not for heart attacks or non-external mortality.

Cross-sectional studies may find a significant association between mortality and a specific air pollutant for any of several reasons:

- The association may reflect a non-zero integral of the acute effects of that pollutant over the period of study.
- The association may reflect a chronic effect from long-term exposures.
- The association may have resulted from confounding, either with another pollutant, with the characteristics of the sources that produced that pollutant (occupational hazards or exposures), or with human elements spatially associated with pollution sources such as differential migration of the healthy, less desirable housing near sources, or other socioeconomic factors.

The studies reviewed above probably all reflect some varying combinations of these possibilities.

Some of the prospective studies demonstrated that including additional pollutant exposures in a statistical model (smoking, occupational exposure) not reflected in the outdoor measurements leads to a stronger statistical mortality relationship with the outdoor measurements. This suggests two possibilities (there may be others):

- The indoor and outdoor exposures may reinforce each other and thus may have similar physiological effects. This may provide some clues as to the most likely of several collinear outdoor pollutants. The responses could be either chronic or acute.
- The indoor or occupational exposures may have created a disease state (independent of the outdoor exposures) that makes the individual more susceptible to outdoor pollution effects.

Distinguishing between these two scenarios will likely require additional research, probably including temporal studies of long-term changes in air quality in different places.

At this time, the results of the long-term studies provide support for the existence of short-term increases in mortality which are not subsequently canceled by decreases below normal rates, as well as for the existence of chronic effects above and beyond the acute PM exposures. Also,

they provide no convincing evidence as to the specific pollutant(s) involved, and they do not rule out the existence of pollutant thresholds. Displacement of mortality on a time scale of one or more years is difficult to infer from ordinary population-based studies because there are a variety of other factors that are also affecting changes in mortality rates. Some long-term changes include demographic changes in the affected population, and changes in the incidence of disease and in cause-specific mortality because of changes in the health care system. The extent to which changes in the relation between mortality rate and air pollution may be confounded with changes in these other factors is uncertain. Prospective studies can in principle account for some of the more important individual risk factors, but the advantage of the prospective design may be lost if changes in individual or personal health risk factors such as smoking status, exercise, habits, and obesity are not included as time-varying covariates in the analyses of the data. These factors may also differ significantly among communities. Long-term changes in mortality could also in principle be detected by changes in air pollution over a shorter time scale than the changes in demographics and in baseline mortality rates.

The chronic exposure studies, taken together, suggest that there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles, and that at least some fraction of these deaths are likely to occur between acute exposure episodes. If this interpretation is correct, then at least some individuals may experience some years of reduction of life as a consequence of PM exposure. Unfortunately, without knowing the age and the prior disease state of the decedents, it is not obvious that this information can be usefully quantified.

12.7.2 Morbidity Effects of PM Exposure

Several morbidity health effect endpoints have been studied to examine their association with PM exposure. These studies provide a measure of the respiratory morbidity status of a community in relation to PM exposure. Principle endpoints include hospitalization for a respiratory illness, respiratory symptoms and disease, and changes in lung function. The relationship with these endpoints and PM exposure indicates that ambient exposure to PM impacts the respiratory system. Acute exposure studies show an effect more than chronic exposure studies, but more recent chronic studies are also indicative of an effect. No relationship between acute exposures and chronic health outcomes have been demonstrated.

Hospitalization

Potentially, the most severe morbidity measure is hospitalization for respiratory and cardiovascular illness diagnosis, especially for COPD and pneumonia specifically. This outcome is coherent with the mortality PM relationship discussed above. The hospitalization studies usually compared daily fluctuations in admissions about a long term (e.g., 19 day) moving average. These fluctuations were regressed on PM estimates for the time period immediately preceding or concurrent with the admissions. Some authors considered lags up to 5 days, but the best predictor usually was the most recent exposure. Some morbidity outcomes associated with hospitalization may be appropriately associated with concurrent admission, while others may require several days of progression to end in an admission. Exposure-response lag periods are not yet well examined for hospital admissions related to PM exposures. Both COPD and pneumonia hospitalization studies show moderate but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The admission studies of respiratory and cardiovascular disease show a similar effect. The hospitalization studies in general use similar analysis methodologies. There is evidence of a relationship to heart disease, but the estimated relative risks are somewhat smaller than those for respiratory endpoints. Overall, these studies are indicative of morbidity effects being related to PM exposure (see Figure 12-1).

While a substantive number of hospitalizations for respiratory related illnesses occur in those $\geq$65 years of age, there are also numerous hospitalizations for those under 65 years of age. Several of the PM_{10} hospitalization studies restricted their analysis by age of the individuals. These studies are clearly indicative of health outcomes related to PM for individuals $\geq$65 years of age, but did not explicitly examine other age groups that would allow directly comparable estimates as some mortality studies did. The limited available analyses examining young age groups, especially children $\leq$14 years of age, constrain possible conclusions about this age group. Studies by Thurston et al. (1992, 1994a,b) and Burnett et al. (1994, 1995) examining acid aerosols and sulphates however did show results differing by age.

The EPA ozone criteria document (U.S. Environmental Protection Agency, 1996) examines several of these same studies for an O_3 effect; it concludes that, collectively, the specific studies evaluated indicate that ambient O_3 often has a significant effect on hospital admissions for asthma and other respiratory causes (with a relative risk ranging from 1.1 to 1.36/100 ppb O_3). The present PM document examines a broader group of studies, which collectively are indicative of

consistent PM effects on hospital admissions for all respiratory causes (COPD, pneumonia, etc.) and for cardiovascular causes. Also, in a very recently reported study which used two pollutant models to evaluate which pollutants made contributions to explaining respiratory hospital admissions, the PM_{10} and O_3 associations appeared to be independent of each other, with no reduction in the relative risk for one pollutant after control for the other.

Respiratory Illness Studies

Acute respiratory illness and the factors determining its occurrence and severity are important public health concerns. This effect is of public health importance because of the widespread potential for exposure to PM and because the occurrence of respiratory illness is common. Of added importance is the fact that recurrent childhood respiratory illness may be a risk factor for later susceptibility to lung damage.

The PM studies generally used several different standard respiratory questionnaires that evaluated respiratory health by asking questions about each child's and adult's respiratory disease and symptom experience daily, weekly or over a longer recall period. The reported symptoms and diseases characterize respiratory morbidity in the cohorts studied. Respiratory morbidity typically includes specific diseases such as asthma and bronchitis, and broader syndromes such as upper and lower respiratory illnesses.

Acute respiratory illness studies typically include several different endpoints, but most investigators reported results for at least two of: (1) upper respiratory illness, (2) lower respiratory illness, or (3) cough. The following relative risks are all estimated for an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. The studies of upper respiratory illness do not show a consistent relationship with PM. Two of the studies showed no effect, three studies estimated an odds ratio near 1.2, and one study estimated the odds ratio of 1.55. Some of inconsistency could be explained by the fact that the studies included very different populations. The studies of lower respiratory disease gave odds ratios which ranged from 1.10 to 1.28 except for the Six-Cities study which gave a value over 2.0. Although the lower respiratory disease studies also include a variety of populations, it is difficult to explain the large range of estimates. The studies of cough were more consistent, having odds ratios ranging from 0.98 to 1.51. Again, the Six City study produced the largest value. The second highest value was that of a Utah study at 1.29.

All three endpoints had the same general pattern of results. Nearly all odds ratios were positive, and the 95% confidence intervals for about half were statistically larger than 1.0 (i.e., they were statistically significant at $p < 0.05$). Each endpoint had one study with a very high odds ratio. This can be contrasted with the hospital admission studies, which all resulted in very similar estimates. There are several factors which could account for this. The respiratory disease studies used a wide variety of designs and, as a result, the models for analysis were also varied. Finally, the populations included several different subgroups, whereas the hospitalization studies tended to include similar populations. There were few studies of respiratory symptoms in adults as compared with those in children.

Acute exposures to PM are associated with increased reporting of respiratory symptoms and with small decrements in several measures of lung function. As a consequence, cross-sectional studies of the relationship between long-term exposure to PM (or any air pollutant) and consequent chronic effects on respiratory function and/or respiratory symptoms may be limited by the inability to control for effects of recent exposures on function and symptoms. Moreover, such studies are further handicapped by: (1) limited or no ability to characterize accurately lifetime exposure to PM other than through "area-based" ecological assignments or assignments inferred from short-term, acute measurements; and (2) their inherent limited ability to characterize correctly other relevant exposure histories (e.g., past histories of respiratory illnesses, passive exposure to tobacco smoke products, active smoking in older subjects, etc.).

Longitudinal studies offer numerous obvious advantages over cross-sectional studies in terms of PM exposure characterization and characterization of relevant covariates. Nonetheless, to the extent to which such studies base their inference with regard to the occurrence of long-term morbidity on effects observed over relatively short durations of cohort follow-up (e.g., incident respiratory illness in relationship to ambient PM, short-term relationship between ambient PM and lung function, etc.), their results need to be viewed with circumspection. These approaches do not definitively establish long-term exposure effects but only suggest the coherence of the possibility of such long-term effects.

Three chronic respiratory disease studies were based on a similar type of questionnaire but were done by Harvard University at three different times as part of the Six Cities and 24-Cities Studies. The studies provide data on the relationship of chronic respiratory disease to PM. All three studies suggest a chronic effect of PM on respiratory disease. The analyses for chronic

cough, chest illness and bronchitis tended to be significantly positive. These studies suffer from the usual difficulty of cross sectional studies. The effect of particulate matter is based on variations in exposure which are determined by the different number of locations. The results seen in all studies were consistent with a PM gradient, but it is difficult to separate out clearly the effects of PM versus any other factors or pollutants which have the same gradient. The recent 24 North American City study is strongly suggestive of an effect on bronchitis from acidic particles or from PM which is consistent with the results of the Six Cities study and thus tends to support the gradient observed.

Pulmonary Function Studies

Pulmonary function studies are part of any comprehensive investigation of possible air pollutant effects. Guidelines for standardized testing procedures and for reference values and interpretative strategies of lung function tests exist. Various factors are important determinants of lung function measures. Lung function in childhood is primarily related to age and, especially, to general stature (as measured by height). The growth patterns differ between males and females. Lung function begins to decline with age in the 3rd to 4th decades and continues to do so monotonically as people age. Cigarette smoking, the presence of COPD and, in some cases, asthma are some factors related to more rapid declines in lung function in adults. Environmental factors undoubtedly influence the natural history of the growth and decline of lung function.

Pulmonary function results are somewhat easier to compare because most studies used peak flow (PEFR) or forced expiratory volume (FEV) as the health end-point measure. Acute pulmonary function studies (summarized in Figure 12-6) are suggestive of a short term effect resulting from particulate pollution. Peak flow rates show decreases in the range of 30 to 40 ml/sec resulting from an increase of 50 µg/m ^{3} in PM_{10} or its equivalent. The results appear to be larger in symptomatic groups such as asthmatics. The effects are seen across a variety of study designs, authors, and analysis methodologies. Effects using FEV_1 or FVC as endpoints are less consistent. For comparison, a study of over 16,000 children found that maternal smoking decreased a child's FEV by 10 - 30 ml. An estimate of the effect of PM on pulmonary function in adults found a 29 (±10) ml decrease in FEV_1 per 50 $\mu g/m^3$ increase in PM_{10}, which is similar in magnitude to the changes found in children.

The chronic pulmonary function studies are less numerous than the acute studies. The Six City studies, which had good monitoring data, found no statistically significant PM effect. However, another recent paper found a small but significant decrease in FVC in healthy non-smokers. Yet another recent study is strongly indicative of a PM effect either from acidic particles or from PM itself. Cross sectional studies require very large sample sizes to detect differences because the studies cannot eliminate person to person variation which is much larger than the within person variation. Thus, the lack of statistical significance in some long-term studies cannot be taken as proof of no effect.

Overall, the morbidity studies as a group qualitatively indicate that acute PM exposures are associated with hospitalization admission for respiratory and cardiovascular disease, increased levels of respiratory symptoms and disease, and pulmonary function decrements. The quantitative magnitude of these relationships and their public health meaning are important aspects to consider.

12.7.3 Comparison of Human Health Effects of PM_{10} Versus $PM_{2.5}$ Exposure

Recent reanalyses of the Six City Study by Schwartz et al. (1996) evaluated the effects of using fine particles (FP = $PM_{2.5}$), inhalable particles (PM_{15}), or coarse particles (CP = PM_{15} - $PM_{2.5}$) as exposure indices. The results were transformed to standard increments of 25 µg/m^3 $PM_{2.5}$ and 50 µg/m^3 PM_{15}, and 25 µg/m^3 for CP, with results for short-term (24-h) PM exposures as depicted earlier in Figure 12-33. Across the six cities, $PM_{2.5}$ was the most predictive of the three PM indices for daily mortality RR increases except in Steubenville, where a more significant CP effect was found (although the FP effect size was as large as in most other cities). In spite of very considerable differences among the cities in terms of climate and demographics, the FP effect sizes were rather consistent. The CP effect sizes were positive, small, and not significant except in Steubenville (positive, significant) and Topeka (negative, nearly significant). In some cases, CP may need to be considered as well as FP in evaluating PM health risks. Since PM_{15} was the sum of FP and CP, it had an intermediate significance, with positive and significant effects except for Portage and Topeka. The St. Louis and Eastern Tennessee associations for PM_{15} and FP were both significant, possibly because of the use of nonparametric smoothers to adjust for weather and time trends.

Relationships between chronic PM exposures indexed by different particle size indicators (PM_{15}, $PM_{2.5}$, PM_{15} - $PM_{2.5}$) and mortality effects as observed in the Harvard Six City Study were earlier depicted graphically in Figure 12-8. More specifically, the adjusted risks are plotted in Figure 12-8, so as to emphasize the increasing correlation of long-term mortality with PM as the size cut of the particles decreases. The figure shows a modest positive association between RR and TSP, but a stronger association between RR and inhalable particles (IP or PM_{15}) and a weaker association between RR and non-inhalable particles (TSP-IP) than between RR and TSP. The figure also shows that there is a stronger association between RR and IP, although the coarse particle relationship is almost linear if Topeka is dropped. The figure also shows that both sulfate and non-sulfate components of fine particles appear to be closely associated with increased PM-related RR.

While numerous morbidity studies have been conducted examining PM health effects for PM_{10} as discussed above, limited numbers of studies have been published that examine fine particles such as $PM_{2.5}$. The most direct comparison of the effect of PM_{10} to $PM_{2.5}$ results when studies include both exposure measures in their analyses. For acute exposure studies, this occurred in the Six City study, the Tucson study, and the Uniontown study. None of these studies could directly show that one of these measures was a significantly better predictor than the other. The Six City study suggested that PM_{10} was a better predictor of respiratory disease. The Tucson study suggested that $PM_{2.5}$ was a better predictor of lung function change. The Uniontown study used $PM_{2.5}$, H^+, and $SO_4^=$ values in their analysis, but not PM_{10} which may have been due to the fact that the PM_{10} values were not available as 12 h averages whereas the other pollutants were.

Two other studies used $PM_{2.5}$ as a measure of particulate exposure. A study of respiratory disease in Denver found an effect that fell in the middle of the range of effects found by the PM_{10} studies. A study of lung function found a slightly larger effect for asthmatics and slightly smaller effect for non-asthmatics when compared with the PM_{10} studies.

Two recent chronic exposure studies provide results for PM_{10}, $PM_{2.1}$, and particulate acidity. One respiratory symptoms study in 24 North American communities reported that children living in communities with the highest levels of particle strong acidity were significantly more likely (OR = 1.66, 95% CI = 1.11, 2.48) to report at least one episode of bronchitis in the past year compared to children living in communities with the lowest levels of acidity. For $PM_{2.1}$, the odds

ratio for bronchitis was 1.50 (95% CD = 0.91, 2.47). No other respiratory symptoms were significantly associated with any of the pollutants. In particular, there was no evidence that the presence of asthma or asthmatic symptoms was associated with the measured pollutants. No sensitive subgroups were identified. The strong correlations of several pollutants in this study, especially particle strong acidity in the sulfate (r = 0.90) and $PM_{2.1}$ (r = 0.82), make it difficult to distinguish the agent of interest.

A study of pulmonary function test results from 22 North American communities described above indicated that a 52 nmole/m^3 difference in annual mean particle strong acidity was associated with a 3.5% deficit in adjusted FVC and a 3.1% deficit in adjusted FEV_1. The deficit was larger (but not statistically larger) in lifelong residents of their communities. Deficits were also found in PEFR and MMEFR although these deficits were not statistically significant. Ratios of FEV and FVC were not statistically significant. Slightly smaller deficits were seen using total sulfate, $PM_{2.1}$, and PM_{10} as pollutant exposure measures, and these deficits were also statistically significant. The data did not allow for the separation of effects of the various particulate matter exposures.

These few studies on $PM_{2.5}$ show effects that are difficult to separate both from PM_{10} measures and acid aerosols measures which are briefly discussed in the next section. The $PM_{2.5}$ studies do show effects related to exposure to the fine fraction. The high correlation between $PM_{2.5}$, PM_{10}, and acid aerosols may make it very difficult to separate out differences.

Health Effects of Acid Aerosols

While most epidemiology studies of PM measure or estimate mass of PM, several studies measured the mass of acid aerosols. Presently this represents the main chemical characterization of PM. However, this mass would primarily be found in the fine fraction of PM, that is $PM_{2.5}$.

Earlier and present-day studies suggest that there can be both acute and chronic effects by strongly acidic PM on human health. Studies of historical pollution for episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that extremely elevated daily acid aerosol concentrations may be associated with excess acute human mortality when present as a co-pollutant with elevated concentrations of PM and SO_2. In addition, significant associations were found between acid aerosols and mortality in London during non-episode pollution levels ($\leq$ 7.5 $\mu g/m^3$ as H_2SO_4, or $\leq$ approximately 150 nmoles/m^3 H^+), though these associations could not

be separated from those for BS or SO_2 (Lippman and Ito, 1995). The attempts to-date to associate present-day levels of acidic aerosols with acute and chronic mortality were unable to do so, but there may not have been a sufficiently long series of H^+ data to detect H^+ associations. Increased hospital admissions for respiratory causes were also documented during the London Fog episode of 1952, and this association has now been observed under present-day conditions, as well. In these studies, H^+ effects were estimated to be the largest during 1 to 3-day acid aerosol episodes ($H^+ \geq 10\ \mu g/m^3$ as H_2SO_4, or $\approx$200 nmoles/m^3 H^+), which occur roughly 2 to 3 times per year in eastern North America. These studies suggest that present-day strongly acidic aerosols can represent a portion of PM which is particularly associated with significant acute respiratory disease health effects in the general public.

Results from recent acute symptoms and lung function studies of healthy children indicate the potential for acute acidic PM effects in this population. The 6-City study of diaries kept by parents of children's respiratory and other illness show H^+ associations with lower respiratory symptoms at H^+ above 110 moles/m^3. Some, but not all, recent summer camp and school children studies of lung function have also indicated significant associations between acute exposures to acidic PM and decreases in the lung function of children independent of those associated with O_3.

Studies of the effects of chronic H^+ exposures on children's respiratory symptoms and lung function are generally suggestive of effects due to chronic H^+ exposure. Preliminary analyses of bronchitis prevalence rates as reported across the 6-City study locales were found to be more closely associated with average H^+ concentrations than with PM in general. Furthermore, in a study of children in 24 U.S. and Canadian communities in which the analysis was adjusted for the effects of gender, age, parental asthma, parental education, and parental allergies, bronchitic symptoms were confirmed to be significantly associated with strongly acidic PM (relative odds = 1.66, 95% CI: 1.11 to 2.48). It was also found in the 24-Cities study that mean FVC and $FEV_{1.0}$ were lower in locales having high particle strong acidity. Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children. The acid levels, however, were highly correlated to other PM indicators such as $PM_{2.1}$, as noted above.

REFERENCES

Abbey, D. E.; Mills, P. K.; Petersen, F. F.; Beeson, W. L. (1991a) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. Environ. Health Perspect. 94: 43-50.

Abbey, D. E.; Moore, J.; Petersen, F.; Beeson, L. (1991b) Estimating cumulative ambient concentrations of air pollutants: description and precision of methods used for an epidemiological study. Arch. Environ. Health 46: 281-287.

Abbey, D. E.; Petersen, F.; Mills, P. K.; Beeson, W. L. (1993) Long-term ambient concentrations of total suspended particulates, ozone, and sulfur dioxide and respiratory symptoms in a nonsmoking population. Arch. Environ. Health 48: 33-46.

Abbey, D. E.; Lebowitz, M. D.; Mills, P. K.; Petersen, F. F.; Beeson, W. L.; Burchette, R. J. (1995a) Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 19-34.

Abbey, D. E.; Ostro, B. E.; Petersen, F.; Burchette, R. J. (1995b) Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM2.5) and other air pollutants. J. Exp. Anal. Environ. Epidemiol. 5: 137-159.

Abbey, D. E.; Ostro, B. E.; Fraser, G.; Vancuren, T.; Burchette, R. J. (1995c) Estimating fine particulates less that 2.5 microns in aerodynamic diameter (PM2.5) from airport visibility data in California. J. Exp. Anal. Environ. Epidemiol. 5: 161-180.

Ackermann-Liebrich, U.; Leuenberger, P.; Schwartz, J.; Schindler, C.; Monn, C.; Bolognini, B.; Bongard, J. P.; Brändli, O.; Domenighetti, G.; Elsasser, S.; Grize, L.; Karrer, W.; Keller, R.; Keller-Wossidlo, H.; Künzli, N.; Martin, B. W.; Medici, T. G.; Perruchoud, A. P.; Schöni, M. H.; Tschopp, J. M.; Villiger, B.; Wüthrich, B.; Zellweger, J. P.; Zemp, E. (1996) Lung function and long term exposure to air pollutants in Switzerland. Am. J. Respir. Crit. Care Med: submitted.

Akaike, H. (1973) Information theory and an extension of the maximum likelihood principle. In: Petrov, B. N.; Csáki, F., eds. 2nd International symposium on information theory; September 1971; Tsahkadsor, Armenia, USSR. Budapest, Hungary: Akadémiai Kiadó; pp. 267-281.

American Thoracic Society. (1962) Definitions and classification of chronic bronchitis, asthma, and pulmonary emphysema. Am. Rev. Respir. Dis. 85: 762-768.

American Thoracic Society. (1987) Standardization of spirometry—1987 update. Am. Rev. Respir. Dis. 136: 1285-1298.

American Thoracic Society. (1991) Lung function testing: selection of reference values and interpretative strategies Am. Rev. Respir. Dis. 144: 1202-1218.

Anderson, D. O.; Ferris, B. G., Jr. (1965) Air pollution levels and chronic respiratory disease. Arch. Environ. Health 10: 307-311.

Anderson, D. O.; Ferris, B. G., Jr.; Zickmantel, R. (1964) Levels of air pollution and respiratory disease in Berlin, New Hampshire. Am. Rev. Respir. Dis. 90: 877-887.

Arossa, W.; Spinaci, S.; Bugiani, M.; Natale, P.; Bucca, C.; de Candussio, G. (1987) Changes in lung function of children after an air pollution decrease. Arch. Environ. Health 42: 170-174.

Bailey, D. L. R.; Clayton, P. (1982) The measurement of suspended particle and total carbon concentrations in the atmosphere using standard smoke shade methods. Atmos. Environ. 16: 2683-2690.

Bates, D. V. (1992) Health indices of the adverse effects of air pollution: the question of coherence. Environ. Res. 59: 336-349.

Bates, D. V.; Sizto, R. (1983) Relationship between air pollutant levels and hospital admissions in Southern Ontario. Can. J. Public Health 74: 117-122.

Bates, D. V.; Sizto, R. (1986) A study of hospital admissions and air pollutants in southern Ontario. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies, proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 767-777.

Bates, D. V.; Sizto, R. (1987) Air pollution and hospital admissions in southern Ontario: the acid summer haze effect. Environ. Res. 43: 317-331.

Bates, D. V.; Sizto, R. (1989) The Ontario Air Pollution study: identification of the causative agent. Environ. Health Perspect. 79: 69-72.

Beard, C. M.; Yunginger, J. W.; Reed, C. E.; O'Connell, E. J.; Silverstein, M. D. (1992) Interobserver variability in medical record review: an epidemiological study of asthma. J. Clin. Epidemiol. 45: 1013-1020.

Beaumont, J. J.; Leveton, J.; Knox, K.; Bloom, T.; McQuiston, T.; Young, M.; Goldsmith, R.; Steenland, N. K.; Brown, D. P.; Halpern, W. E. (1987) Lung cancer mortality in workers exposed to sulfuric acid mist and other acid mists. JNCI J. Natl. Cancer Inst. 79: 911-921.

Belloc, N. D. (1973) Relationship of health practices and mortality. Prev. Med. 2: 67-81.

Belsley, D. A.; Kuh, E.; Welsch, R. E. (1980) Regression diagnostics: identifying influential data and sources of collinearity. New York, NY: John Wiley & Sons, Inc. (Bradley, R. A.; Kendall, D. G.; Hunter, J. S.; Watson, G. S., eds. Wiley series in probability and mathematical statistics).

Bobak, M.; Leon, D. A. (1992) Air pollution and infant mortality in the Czech Republic, 1986-1988. Lancet (8826): 1010-1014.

Bock, N.; Lippmann, M.; Lioy, P.; Munoz, A.; Speizer, F. E. (1985) The effects of ozone on the pulmonary function of children. In: Lee, S. D., ed. Evaluation of the scientific basis for ozone/oxidants standards: proceedings of an APCA international specialty conference; November 1984; Houston, TX. Pittsburgh, PA: Air Pollution Control Association; pp. 297-308. (APCA international specialty conference transactions: TR-4).

Bouhuys, A.; Beck, G. J.; Schoenberg, J. B. (1978) Do present levels of air pollution outdoors affect respiratory health? Nature (London) 276: 466-471.

Box, G. E. P.; Jenkins, G. M. (1976) Time series analysis: forecasting and control. San Francisco, CA: Holden-Day. (Robinson, E., ed. Holden-Day series in time series analysis and digital processing).

Brancati, F. L.; Chow, J. W.; Wagener, M. M.; Vacarello, S. J.; Yu, V. L. (1993) Is pneumonia really the old man's friend? Two-year prognosis after community-acquired pneumonia. Lancet (8862): 30-33.

Braun-Fahrländer, C.; Ackermann-Liebrich, U.; Schwartz, J.; Gnehm, H. P.; Rutishauser, M.; Wanner, H. U. (1992) Air pollution and respiratory symptoms in preschool children. Am. Rev. Respir. Dis. 145: 42-47.

Britten, N.; Davies, J. M. C.; Colley, J. R. T. (1987) Early respiratory experience and subsequent cough and peak expiratory flow rate in 36 year old men and women. Br. Med. J. 294: 1317-1320.

Brunekreef, B.; Kinney, P. L.; Ware, J. H.; Dockery, D.; Speizer, F. E.; Spengler, J. D.; Ferris, B. G., Jr. (1991) Sensitive subgroups and normal variation in pulmonary function response to air pollution episodes. Environ. Health Perspect. 90: 189-193.

Buffington, J.; Chapman, L. E.; Schmeltz, L. M.; Kendal, A. P. (1993) Do family physicians make good sentinels for influenza? Arch. Fam. Med. 2: 859-865.

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burrows, B.; Lebowitz, M. D. (1975) Characteristics of chronic bronchitis in a warm, dry region. Am. Rev. Respir. Dis. 112: 365-370.

Burton, R. M.; Suh, H. H.; Koutrakis, P. (1996) Spatial variation in particulate concentrations within metropolitan Philadelphia. Environ. Sci. Technol. 30: 400-407.

Carr, W.; Zeitel, L.; Weiss, K. (1992) Variations in asthma hospitalizations and deaths in New York City. Am. J. Public Health 82: 59-65.

Cass, G. R.; Conklin, M. H.; Shah, J. J.; Huntzicker, J. J.; Macias, E. S. (1984) Elemental carbon concentrations: estimation of an historical data base. Atmos. Environ. 18: 153-162.

Chanock, R. M.; Parrott, R. H. (1965) Acute respiratory disease in infancy and childhood: present understanding and prospects for prevention. Pediatrics 36: 21-39.

Chanock, R. M.; McIntosh, K.; Murphy, B. R.; Parrott, R. H. (1989) Respiratory syncytial virus. In: Evans, A. S., ed. Viral infections of humans: epidemiology and control. 3rd ed. New York, NY: Plenum Publishing Corporation; pp. 525-544.

Chapman, R. S.; Henderson, F. W.; Clyde, W. A., Jr.; Collier, A. M.; Denny, F. W. (1981) The epidemiology of tracheobronchitis in pediatric practice. Am. J. Epidemiol. 114: 786-797.

Chapman, R. S.; Calafiore, D. C.; Hasselblad, V. (1985) Prevalence of persistent cough and phlegm in young adults in relation to long-term ambient sulfur oxide exposure. Am. Rev. Respir. Dis. 132: 261-267.

Chappie, M.; Lave, L. (1982) The health effects of air pollution: a reanalysis. J. Urban Econ. 12: 346-376.

Charlton, A.; Blair, V. (1989) Absence from school related to children's and parental smoking habits. Br. Med. J. 298: 90-92.

Chestnut, L. G.; Schwartz, J.; Savitz, D. A.; Burchfiel, C. M. (1991) Pulmonary function and ambient particulate matter: epidemiological evidence from NHANES I. Arch. Environ. Health 46: 135-144.

Cifuentes, L.; Lave, L. B. (1996) Association of daily mortality and air pollution in Philadelphia, 1983-1988. J. Air Waste Manage. Assoc.: in press.

Cleveland, W. S. (1979) Robust locally weighted regression and smoothing scatterplots. J. Am. Stat. Assoc. 74: 829-836.

Cochran, W. G. (1968) Errors of measurement in statistics. Technometrics 10: 637-666.

Cohen, B. L. (1994) Invited commentary: in defense of ecologic studies for testing a linear-no threshold theory. Am. J. Epidemiol. 139: 765-768.

Commins, B. T. (1963) Determination of particulate acid in town air. Analyst (London) 88: 364-367.

Commins, B. T.; Waller, R. E. (1967) Observations from a ten-year-study of pollution at a site in the city of London. Atmos. Environ. 1: 49-68.

Cooper, D. E.; Hamilton, W. C. (1979) Atmospheric sulfates and mortality—the phantom connection. Min. Congr. J. 65(1): 49-55.

Cox, C. (1987) Threshold dose-response models in toxicology. Biometrics 43: 511-523.

Crane, J.; Pearce, N.; Burgess, C.; Woodman, K.; Robson, B.; Beasley, R. (1992) Markers of risk of asthma death or readmission in the 12 months following a hospital admission for asthma. Int. J. Epidemiol. 21: 737-744.

Crump, K. S. (1984a) A new method for determining allowable daily intakes. Fundam. Appl. Toxicol. 4: 854-871.

Crump, K. S. (1984b) Mechanisms leading to dose-response models. In: Ficci, P. F., ed. Principles of health risk assessment. Englewood Clifts, NJ: Prentice-Hall, Inc.; pp. 235-277.

Crump, K. S.; Howe, R. B. (1985) A review of methods for calculating statistical confidence limits in low dose extrapolation. In: Clayson, D. B.; Krewski, D.; Munro, I., eds. Toxicological risk assessment: v. I, biological and statistical criteria. Boca Raton, FL: CRC Press, Inc.; pp. 187-203.

Damokosh, A. I.; Spengler, J. D.; Dockery, D. W.; Ware, J. H.; Speizer, F. E. (1993) Effects of acidic particles on respiratory symptoms in 7 US communities. Am. Rev. Respir. Dis. 147: A632.

Dassen, W.; Brunekreef, B.; Hoek, G.; Hofschreuder, P.; Staatsen, B.; De Groot, H.; Schouten, E.; Biersteker, K. (1986) Decline in children's pulmonary function during an air pollution episode. J. Air Pollut. Control Assoc. 36: 1223-1227.

Delfino, R. J.; Becklake, M. R.; Hanley, J. A. (1994a) The relationship of urgent hospital admissions for respiratory illnesses to photochemical air pollution levels in Montreal. Environ. Res. 67: 1-19.

Delfino, R. J.; Becklake, M. R.; Hanley, J. A.; Singh, B. (1994b) Estimation of unmeasured particulate air pollution data for an epidemiological study of daily respiratory morbidity. Environ. Res. 67: 20-38.

Denny, F. W.; Clyde, W. A. (1986) Acute lower respiratory tract infections in nonhospitalized children. J. Pediatr. (St. Louis) 108: 635-646.

Denny, F. W.; Murphy, T. F.; Clyde, W. A., Jr.; Collier, A. M.; Henderson, F. W. (1983) Croup: an 11-year study in a pediatric practice. Pediatrics 71: 871-876.

Derriennic, F.; Richardson, S.; Mollie, A.; Lellouch, J. (1989) Short-term effects of sulphur dioxide pollution on mortality in two French cities. Int. J. Epidemiol. 18: 186-197.

Dinman, B. D. (1972) "Non-concept" of "no-threshold": chemicals in the environment. Science (Washington, DC) 175: 495-497.

Dockery, D. W. (1993) Epidemiological study design for investigating respiratory health effects of complex air pollution mixtures. Environ. Health Perspect. 101(suppl. 4): 187-191.

Dockery, D. W. (1995) Particle/mortality associations in St. Louis and eastern Tennessee: elaboration of published results. Prepared for: EPA critical evaluation workshop on particulate matter-mortality epidemiology studies;

November 1994; Raleigh, NC. Boston, MA: Harvard School of Public Health, Department of Environmental Health.

Dockery, D. W.; Pope, C. A., III. (1994a) Air pollution and mortality: the authors reply [letter]. N. Engl. J. Med. 330: 1238.

Dockery, D. W.; Pope, C. A., III. (1994b) Acute respiratory effects of particulate air pollution. Annu. Rev. Public Health 15: 107-132.

Dockery, D. W.; Schwartz, J. (1992) The authors' response to Waller and Swan. Am. J. Epidemiol. 135: 23-25.

Dockery, D. W.; Ware, J. H.; Ferris, B. G., Jr.; Speizer, F. E.; Cook, N. R.; Herman, S. M. (1982) Change in pulmonary function in children associated with air pollution episodes. J. Air Pollut. Control Assoc. 32: 937-942.

Dockery, D. W.; Berkey, C. S.; Ware, J. H.; Speizer, F. E.; Ferris, B. G., Jr. (1983) Distribution of forced vital capacity and forced expiratory volume in one second in children 6 to 11 years of age. Am. Rev. Respir. Dis. 128: 405-412.

Dockery, D. W.; Ware, J. H.; Ferris, B. G., Jr.; Glicksberg, D. S.; Fay, M. E.; Spiro, A., III; Speizer, F. E. (1985) Distribution of forced expiratory volume in one second and forced vital capacity in healthy, white, adult never-smokers in six U.S. cities. Am. Rev. Respir. Dis. 131: 511-520.

Dockery, D. W.; Speizer, F. E.; Stram, D. O.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr. (1989) Effects of inhalable particles on respiratory health of children. Am. Rev. Respir. Dis. 139: 587-594.

Dockery, D. W.; Schwartz, J.; Spengler, J. D. (1992) Air pollution and daily mortality: associations with particulates and acid aerosols. Environ. Res. 59: 362-373.

Dockery, D. W.; Pope, C. A., III; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G., Jr.; Speizer, F. E. (1993) An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329: 1753-1759.

Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. Environ. Health Perspect: in press.

Dodge, R.; Solomon, P.; Moyers, J.; Hayes, C. (1985) A longitudinal study of children exposed to sulfur oxides. Am. J. Epidemiol. 121: 720-736.

Doll, R.; Peto, R.; Hall, E.; Wheatley, K.; Gray, R. (1994) Mortality in relation to consumption of alcohol: 13 years' observations on male British doctors. Br. Med. J. 309: 911-918.

Duclos, P.; Sanderson, L. M.; Lipsett, M. (1990) The 1987 forest fire disaster in California: assessment of emergency room visits. Arch. Environ. Health 45: 53-58.

Dusseldorp, A.; Kruize, H.; Brunekreef, B.; Hofschreuder, P.; de Meer, G.; van Oudvorst, A. B. (1994) Associations of PM10 and airborne iron with respiratory health of adults living near a steel factory. Am. J. Respir. Crit. Care Med. 152: 1932-1939.

Euler, G. L.; Abbey, D. E.; Magie, A. R.; Hodgkin, J. E. (1987) Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total suspended particulates and sulfur dioxide in California Seventh-Day Adventist residents. Arch. Environ. Health 42: 213-222.

Euler, G. L.; Abbey, D. E.; Hodgkin, J. E.; Magie, A. R. (1988) Chronic obstructive pulmonary disease symptom effects of long-term cumulative exposure to ambient levels of total oxidants and nitrogen dioxide in California Seventh-day Adventist residents. Arch. Environ. Health 43: 279-285.

European Myocardial Infarction Project Group. (1993) Prehospital thrombolytic therapy in patients with suspected acute myocardial infarction. N. Engl. J. Med. 329: 383-389.

Evans, J. S.; Tosteson, T.; Kinney, P. L. (1984a) Cross-sectional mortality studies and air pollution risk assessment. Environ. Int. 10: 55-83.

Evans, J. S.; Kinney, P. L.; Koehler, J. L.; Cooper, D. W. (1984b) The relationship between cross-sectional and time series studies. J. Air Pollut. Control Assoc. 34: 551-553.

Fairley, D. (1990) The relationship of daily mortality to suspended particulates in Santa Clara county, 1980-86. Environ. Health Perspect. 89: 159-168.

Fairley, D. (1994) Mortality and particulate exposure in Santa Clara County, CA 1980-86. Santa Clara, CA: Bay Area Air Quality Management District.

Federal Register. (1987) Revisions to the national ambient air quality standards for particulate matter. F. R. (July 1) 52: 24634-24669.

Fedson, D. S.; Wajda, A.; Nicol, J. P.; Roos, L. L. (1992) Disparity between influenza vaccination rates and risks for influenza-associated hospital discharge and death in Manitoba in 1982-1983. Ann. Intern. Med. 116: 550-555.

Ferrand, E. (1978) Air quality trends in New York City. Bull. N.Y. Acad. Med. 54: 1025-1031.

Ferris, B. G., Jr.; Anderson, D. O. (1962) The prevalence of chronic respiratory disease in a New Hampshire town. Am. Rev. Respir. Dis. 86: 165-185.

Ferris, B. G., Jr.; Burgess, W. A.; Worcester, J. (1967) Prevalence of chronic respiratory disease in a pulp mill and a paper mill in the United States. Br. J. Ind. Med. 24: 26-37.

Ferris, B. G., Jr.; Higgins, I. T. T.; Higgins, M. W.; Peters, J. M.; Van Ganse, W. F.; Goldman, M. D. (1971) Chronic nonspecific respiratory disease, Berlin, New Hampshire, 1961-1967: a cross-sectional study. Am. Rev. Respir. Dis. 104: 232-244.

Ferris, B. G., Jr.; Chen, H.; Puleo, S.; Murphy, R. L. H., Jr. (1976) Chronic nonspecific respiratory disease in Berlin, New Hampshire, 1967 to 1973: a further follow-up study. Am. Rev. Respir. Dis. 113: 475-485.

Ferris, B. G., Jr.; Speizer, F. E.; Spengler, J. D.; Dockery, D.; Bishop, Y. M. M.; Wolfson, M.; Humble, C. (1979) Effects of sulfur oxides and respirable particles on human health: methodology and demography of populations in study. Am. Rev. Respir. Dis. 120: 767-779.

Ferris, B. G., Jr.; Ware, J. H.; Spengler, J. D.; Dockery, D. W.; Speizer, F. E. (1986) The Harvard six-cities study. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies: proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 721-730.

Firket, J. (1931) Sur les causes des accidents survenus dans la vallée de la Meuse, lors des brouillards de décembre 1930 [The causes of accidents which occurred in the Meuse Valley during the fogs of December 1930]. Bull. Acad. R. Med. Belg. 11[ser. 5]: 683-741.

Firket, J. (1936) Fog along the Meuse Valley. Trans. Faraday Soc. 32: 1192-1197.

Franklin, C. A.; Burnett, R. T.; Paolini, R. J. P.; Raizenne, M. E. (1985) Health risks from acid rain: a Canadian perspective. Environ. Health Perspect. 63: 155-168.

Gamble, J.; Jones, W.; Hancock, J. (1984a) Epidemiological-environmental study of lead acid battery workers: II. acute effects of sulfuric acid on the respiratory system. Environ. Res. 35: 11-29.

Gamble, J.; Jones, W.; Hancock, J.; Meckstroth, R. L. (1984b) Epidemiological-environmental study of lead acid battery workers: III. chronic effects of sulfuric acid on the respiratory system and teeth. Environ. Res. 35: 30-52.

Gergen, P. J.; Weiss, K. B. (1990) Changing patterns of asthma hospitalization among children: 1979 to 1987. JAMA J. Am. Med. Assoc. 264: 1688-1692.

Gerstman, B. B.; Bosco, L. A.; Tomita, D. K. (1993) Trends in the prevalence of asthma hospitalization in the 5- to 14-year-old Michigan Medicaid population, 1980 to 1986. J. Allergy Clin. Immunol. 91: 838-843.

Gilbert, E. S. (1984) Some effects of random dose measurement errors on analyses of atomic bomb survivor data. Radiat. Res. 98: 591-605.

Glezen, W. P. (1989) Antecedents of chronic and recurrent lung disease: childhood respiratory trouble. Am. Rev. Respir. Dis. 140: 873-874.

Glezen, W. P.; Denny, F. W. (1973) Epidemiology of acute lower respiratory disease in children. N. Engl. J. Med. 288: 498-505.

Gold, D. R.; Tager, I. B.; Weiss, S. T.; Tosteson, T. D.; Speizer, F. E. (1989) Acute lower respiratory illness in childhood as a predictor of lung function and chronic respiratory symptoms. Am. Rev. Respir. Dis. 140: 877-884.

Gordian, M. E.; Morris, S.; Özkaynak, H.; Xue, J.; Spengler, J. (1995) Particulate air pollution and respiratory disease in Anchorage, Alaska. In: Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; pp. 143-166. (A&WMA publication VIP-49).

Gordian, M. E.; Özkaynak, H.; Xue, J.; Morris, S. S.; Spengler, J. D. (1996) Particulate air pollution and respiratory disease in Anchorage, Alaska. Environ. Health Perspect. 104: 209-297.

Greenland, S.; Robins, J. (1994a) Invited commentary: ecologic studies—biases, misconceptions, and counterexamples. Am. J. Epidemiol. 139: 747-760.

Greenland, S.; Robins, J. (1994b) Accepting the limits of ecologic studies: Drs. Greenland and Robins reply to Drs. Piantadosi and Cohen. Am. J. Epidemiol. 139: 769-771.

Greenland, S.; Schlesselman, J. J.; Criqui, M. H. (1986) The fallacy of employing standardized regression coefficients and correlations as measures of effect. Am. J. Epidemiol. 123: 203-208.

Grønbæk, M.; Deis, A.; Sørensen, T. I. A.; Becker, U.; Borch-Johnsen, K.; Müller, C.; Schnohr, P.; Jensen, G. (1994) Influence of sex, age, body mass index, and smoking on alcohol intake and mortality. Br. Med. J. 308: 302-306.

Hasselblad, V.; Creason, J. P.; Nelson, C. J. (1976) Regression using "hockey stick" function. Research Triangle Park, NC: U.S. Environmental Protection Agency, Health Effects Research Laboratory; EPA report no. EPA-600/1-76-024. Available from: NTIS, Springfield, VA; PB-253 576.

Hasselblad, V.; Humble, C. G.; Graham, M. G.; Anderson, H. S. (1981) Indoor environmental determinants of lung function in children. Am. Rev. Respir. Dis. 123: 479-485.

Hasselblad, V.; Eddy, D. M.; Kotchmar, D. J. (1992) Synthesis of environmental evidence: nitrogen dioxide epidemiology studies. J. Air Waste Manage. Assoc. 42: 662-671.

Hastie, T.; Tibshirani, R. (1990) Generalized additive models. London, United Kingdom: Chapman and Hall.

Hausman, J. A.; Ostro, B. D.; Wise, D. A. (1984) Air pollution and lost work. Cambridge, MA: National Bureau of Economic Research; NBER working paper no. 1263.

He, Q.-C.; Lioy, P. J.; Wilson, W. E.; Chapman, R. S. (1993) Effects of air pollution on children's pulmonary function in urban and suburban areas of Wuhan, People's Republic of China. Arch. Environ. Health 48: 382-391.

Hefflin, B. J.; Jalaludin, B.; McClure, E.; Cobb, N.; Johnson, C. A.; Jecha, L.; Etzel, R. A. (1994) Surveillance for dust storms and respiratory diseases in Washington State, 1991. Arch. Environ. Health 49: 170-174.

Hemeon, W. C. L. (1955) The estimation of health hazards from air pollution. AMA Arch. Ind. Health 11: 397-402.

Henderson, F. W.; Clyde, W. A., Jr.; Collier, A. M.; Denny, F. W.; Senior, R. J.; Sheaffer, C. I.; Conley, W. G., III; Christian, R. M. (1979a) The etiologic and epidemiologic spectrum of bronchiolitis in pediatric practice. J. Pediatr. (St. Louis) 95: 183-190.

Henderson, F. W.; Collier, A. M.; Clyde, W. A., Jr.; Denny, F. W. (1979b) Respiratory-syncytial-virus infections, reinfections and immunity: a prospective, longitudinal study in young children. N. Engl. J. Med. 300: 530-534.

Hill, A. B. (1965) The environment and disease: association or causation? Proc. R. Soc. Med. 58: 295-300.

Hochberg, Y.; Tamhane, A. C. (1987) Multiple comparison procedures. New York, NY: John Wiley & Sons, Inc.; pp. 17-133.

Hodgkin, J. E.; Abbey, D. E.; Euler, G. L.; Magie, A. R. (1984) COPD prevalence in nonsmokers in high and low photochemical air pollution areas. Chest 86: 830-838.

Hoek, G. (1992) Acute effects of ambient air pollution episodes on respiratory health of children [thesis]. Wageningen, The Netherlands: Agricultural University of Wageningen.

Hoek, G.; Brunekreef, B. (1993) Acute effects of a winter air pollution episode on pulmonary function and respiratory symptoms of children. Arch. Environ. Health 48: 328-335.

Hoek, G.; Brunekreef, B. (1994) Effects of low-level winter air pollution concentrations on respiratory health of Dutch children. Environ. Res. 64: 136-150.

Hoek, G.; Brunekreef, B. (1995) Effect of photochemical air pollution on acute respiratory symptoms in children. Am. J. Respir. Crit. Care Med. 151: 27-32.

Hudson, D. J. (1966) Fitting segmented curves whose join points have to be estimated. J. Am. Stat. Assoc. 61: 1097-1129.

Hunter, J. E.; Schmidt, F. L. (1989) Methods of meta-analysis: correcting error & bias in research findings. Thousand Oaks, CA: Sage Publications, Inc.

International Electric Research Exchange. (1981) Effects of SO2 and its derivatives on health and ecology: volume I, human health. Palo Alto, CA: Electrical Power Research Institute.

Ishikawa, S.; Bowden, D. H.; Fisher, V.; Wyatt, J. P. (1969) The "emphysema profile" in two midwestern cities in North America. Arch. Environ. Health 18: 660-666.

Ito, K. (1990) An examination of the role of aerosol acidity in historical London, England daily mortality [dissertation]. Syracuse, NY: New York University. Available from: University Microfilms International, Ann Arbor, MI; AAD91-13012.

Ito, K.; Thurston, G. D. (1996) Daily PM10/mortality associations: an investigation of at-risk sub-populations. J. Exposure Anal. Environ. Epidemiol.: in press.

Ito, K.; Thurston, G. D.; Hayes, C.; Lippmann, M. (1993) Associations of London, England, daily mortality with particulate matter, sulfur dioxide, and acidic aerosol pollution. Arch. Environ. Health 48: 213-220.

Ito, K.; Kinney, P.; Thurston, G. D. (1995) Variations in PM-10 concentrations within two metropolitan areas and their implications for health effects analyses. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 735-745.

Jedrychowski, W.; Krzyżanowski, M. (1989) Ventilatory lung function and chronic chest symptoms among the inhabitants of urban areas with various levels of acid aerosols: prospective study in Cracow. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 101-107.

Jedrychowski, W.; Becher, H.; Wahrendorf, J.; Basa-Cierpialek, Z. (1990) A case-control study of lung cancer with special reference to the effect of air pollution in Poland. J. Epidemiol. Commun. Health 44: 114-120.

Jenkins, J. S.; Flaker, G. C.; Nolte, B.; Price, L. A.; Morris, D.; Kurz, J.; Petroski, G. F. (1994) Causes of higher in-hospital mortality in women than in men after acute myocardial infarction. Am. J. Cardiol. 73: 319-322.

Johnson, K. G.; Loftsgaarden, D. O.; Gideon, R. A. (1982) The effects of Mount St. Helens volcanic ash on the pulmonary function of 120 elementary school children. Am. Rev. Respir. Dis. 126: 1066-1069.

Johnson, K. G.; Gideon, R. A.; Loftsgaarden, D. O. (1990) Montana Air Pollution Study: children's health effects. J. Off. Stat. 5: 391-407.

Jollis, J. G.; Ancukiewicz, M.; DeLong, E. R.; Pryor, D. B.; Muhlbaier, L. H.; Mark, D. B. (1993) Discordance of databases designed for claims payment versus clinical information systems: implications for outcomes research. Ann. Intern. Med. 119: 844-850.

Kalkstein, L. S. (1991) A new approach to evaluate the impact of climate on human mortality. Environ. Health Perspect. 96: 145-150.

Kalkstein, L. S. (1993a) Direct impacts in cities. Lancet 342: 1397-1399.

Kalkstein, L. S. (1993b) Climate change and human health. U.S. Environmental Protection Agency; cooperative agreement no. CR-817693.

Kalkstein, L. S.; Tan, G.; Skindlov, J. (1987) An evaluation of objective clustering procedures for use in synoptic climatological classification. J. Climate Appl. Meteorol. 26: 717-730.

Kalkstein, L. S.; Barthel, C. D.; Ye, H.; Smoyer, K.; Cheng, S.; Greene, J. S.; Nichols, M. C. (1994) The differential impacts of weather and pollution on human mortality. Newark, DE: University of Delaware, Department of Geography, Center for Climatic Research; November.

Kalkstein, L. S.; Barthel, C. D.; Ye, H.; Smoyer, K.; Cheng, S.; Greene, J. S.; Nichols, M. C. (1995) The impacts of weather and pollution on human mortality. Washington, DC: U.S. Environmental Protection Agency, Office of Policy, Planning, and Evaluation, Climate Change Division; March; cooperative agreement no. CR-817693.

Katsouyanni, K. (1995) PM mortality review. Report to U.S. Environmental Protection Agency, National Center for Environmental Assessment, Research Triangle Park, NC.

Katsouyanni, K.; Karakatsani, A.; Messari, I.; Touloumi, G.; Hatzakis, A.; Kalandidi, A.; Trichopoulos, D. (1990a) Air pollution and cause specific mortality in Athens. J. Epidemiol. Commun. Health 44: 321-324.

Katsouyanni, K.; Hatzakis, A.; Kalandidi, A.; Trichopoulos, D. (1990b) Short-term effects of atmospheric pollution on mortality in Athens. Arch. Hellen. Med. 7: 126-132.

Katsouyanni, K.; Trichopoulos, D.; Kalandidi, A.; Tomos, P.; Riboli, E. (1991) A case-control study of air pollution and tobacco smoking in lung cancer among women in Athens. Prev. Med. 20: 271-278.

Katsouyanni, K.; Pantazopoulou, A.; Touloumi, G.; Tselepidaki, I.; Moustris, K.; Asimakopoulos, D.; Poulopoulou, G.; Trichopoulos, D. (1993) Evidence for interaction between air pollution and high temperature in the causation of excess mortality. Arch. Environ. Health 48: 235-242.

Kenline, P. A. (1962) In quest of clean air for Berlin, New Hampshire. Cincinnati, OH: U.S. Department of Health, Education, and Welfare, Public Health Service; technical report no. SEC TR A62-9.

Kim, Y. S. (1985) Air pollution, climate, socioeconomic status and total mortality in the United States. Sci. Total Environ. 42: 245-256.

Kinney, P. L.; Özkaynak, H. (1991) Associations of daily mortality and air pollution in Los Angeles County. Environ. Res. 54: 99-120.

Kinney, P. L.; Ito, K.; Thurston, G. D. (1995) A sensitivity analysis of mortality/PM_{10} associations in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 59-69.

Kitagawa, T. (1984) Cause analysis of the Yokkaichi asthma episode in Japan. J. Air Pollut. Control Assoc. 34: 743-746.

Klepper, S.; Kamlet, M. S.; Frank, R. G. (1993) Regressor diagnostics for the errors-in-variables model—an application to the health effects of pollution. J. Environ. Econ. Manage. 24: 190-211.

Klerman, L. V. (1988) School absence—a health perspective. Pediatr. Clin. N. Am. 35: 1253-1269.

Koenig, J. Q.; Pierson, W. E.; Horike, M. (1983) The effects of inhaled sulfuric acid on pulmonary function in adolescent asthmatics. Am. Rev. Respir. Dis. 128: 221-225.

Koenig, J. Q.; Larson, T. V.; Hanley, Q. S.; Rebolledo, V.; Dumler, K.; Checkoway, H.; Wang, S.-Z.; Lin, D.; Pierson, W. E. (1993) Pulmonary function changes in children associated with fine particulate matter. Environ. Res. 63: 26-38.

Kornguth, M. L. (1990) School illnesses: who's absent and why? Pediatr. Nurs. 16: 95-99.

Krzyżanowski, M.; Wojtyniak, B. (1982) Ten-year mortality in a sample of an adult population in relation to air pollution. J. Epidemiol. Commun. Health 36: 262-268.

Kunst, A. E.; Looman, C. W. N.; Mackenbach, J. P. (1993) Outdoor air temperature and mortality in the Netherlands: a time-series analysis. Am. J. Epidemiol. 137: 331-341.

Lamm, S. H.; Hall, T. A.; Engel, A.; Rueter, F. H.; White, L. D. (1994) PM_{10} particulates: are they the major determinant of pediatric respiratory admissions in Utah County, Utah (1985-1989). In: Dodgson, J.; McCallum, R. I., eds. Inhaled particles VII: proceedings of an international symposium; September 1991; Edinburgh, United Kingdom. Ann. Occup. Hyg. 38(suppl. 1): 969-972.

Lave, L. B.; Seskin, E. P. (1970) Air pollution and human health: the quantitative effect, with an estimate of the dollar benefit of pollution abatement, is considered. Science (Washington, DC) 169: 723-733.

Lave, L. B.; Seskin, E. P. (1972) Air pollution, climate, and home heating: their effects on U.S. mortality rates. Am. J. Public Health 62: 909-916.

Lave, L. B.; Seskin, E. P. (1977) Air pollution and human health. Baltimore, MD: The Johns Hopkins University Press.

Lawther, P. J.; Waller, R. E.; Henderson, M. (1970) Air pollution and exacerbations of bronchitis. Thorax 25: 525-539.

Leamer, E. E. (1978) Specification searches: ad hoc inference with nonexperimental data. New York, NY: John Wiley & Sons. (Bradley, R. A.; Hunter, J. S.; Kendall, D. G.; Watson, G. S., eds. Wiley series in probability and mathematical statistics).

Lebowitz, M. D.; O'Rourke, M. K.; Dodge, R.; Holberg, C. J.; Corman, G.; Hoshaw, R. W.; Pinnas, J. L.; Barbee, R. A.; Sneller, M. R. (1982) The adverse health effects of biological aerosols, other aerosols, and indoor microclimate on asthmatics and nonasthmatics. Environ. Int. 8: 375-380.

Lebowitz, M. D.; Quackenboss, J. J.; Krzyzanowski, M.; O'Rourke, M. K.; Hayes, C. (1992) Multipollutant exposures and health responses to particulate matter. Arch. Environ. Health 47: 71-75.

Leviton, A.; Bellinger, D.; Allred, E. N.; Rabinowitz, M.; Needleman, H.; Schoenbaum, S. (1993) Pre- and postnatal low-level lead exposure and children's dysfunction in school. Environ. Res. 60: 30-43.

Li, Y.; Roth, H. D. (1995) Daily mortality analysis by using different regression models in Philadelphia County, 1973-1990. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 45-58.

Liang, K.-Y.; Zeger, S. L. (1986) Longitudinal data analysis using generalized linear models. Biometrika 73: 13-22.

Lindley, D. V. (1947) Regression lines and the linear functional relationship. J. R. Stat. Soc. B: 218-224.

Lioy, P. J.; Vollmuth, T. A.; Lippmann, M. (1985) Persistence of peak flow decrement in children following ozone exposures exceeding the national ambient air quality standard. J. Air Pollut. Control Assoc. 35: 1068-1071.

Lioy, P. J.; Spektor, D.; Thurston, G.; Citak, K.; Lippmann, M.; Bock, N.; Speizer, F. E.; Hayes, C. (1987) The design considerations for ozone and acid aerosol exposure and health investigations: the Fairview Lake summer camp—photochemical smog case study. Environ. Int. 13: 271-283.

Lipfert, F. W. (1978) The association of human mortality with air pollution: statistical analyses by region, by age, and by cause of death. Mantua, NJ: Eureka Publications.

Lipfert, F. W. (1980a) Differential mortality and the environment: the challenge of multicollinearity in cross-sectional studies. Energy Sys. Policy 3: 367-400.

Lipfert, F. W. (1980b) Sulfur oxides, particulates, and human mortality: synopsis of statistical correlations. J. Air Pollut. Control Assoc. 30: 366-371.

Lipfert, F. W. (1984) Air pollution and mortality: specification searches using SMSA-based data. J. Environ. Econ. Manage. 11: 208-243.

Lipfert, F. W. (1985) Mortality and air pollution: is there a meaningful connection? Environ. Sci. Technol. 19: 764-770.

Lipfert, F. W. (1988) Exposure to acidic sulfates in the atmosphere: review and assessment. Final report. Palo Alto, CA: Electric Power Research Institute; report no. EPRI EA-6150.

Lipfert, F. W. (1992) An assessment of acid fog. Upton, NY: Brookhaven National Laboratory; report no. BNL-48499.

Lipfert, F. W. (1993a) Community air pollution and mortality: analysis of 1980 data from US metropolitan areas. I. Particulate air pollution. Upton, NY: U.S. Department of Energy, Brookhaven National Laboratory; report no. BNL 48446-R.

Lipfert, F. W. (1994a) Air pollution and community health: a critical review and data sourcebook. New York, NY: Van Nostrand Reinhold.

Lipfert, F. W. (1994b) Filter artifacts associated with particulate measurements: recent evidence and effects on statistical relationships. Atmos. Environ. 28: 3233-3249.

Lipfert, F. W. (1995) Estimating air pollution-mortality risks from cross-sectional studies: prospective vs. ecologic study designs. In: Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; pp. 78-102. (A&WMA publication VIP-49).

Lipfert, F. W.; Hammerstrom, T. (1992) Temporal patterns in air pollution and hospital admissions. Environ. Res. 59: 374-399.

Lipfert, F. W.; Morris, S. C. (1991) Air pollution benefit-cost assessment. Science (Washington, DC) 253: 606.

Lipfert, F. W.; Wyzga, R. E. (1995a) Uncertainties in identifying responsible pollutants in observational epidemiology studies. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 671-689.

Lipfert, F. W.; Wyzga, R. E. (1995b) Air pollution and mortality: issues and uncertainties. J. Air Waste Manage. Assoc. 45: 949-966.

Lipfert, F. W.; Malone, R. G.; Daum, M. L.; Mendell, N. R.; Yang, C.-C. (1988) A statistical study of the macroepidemiology of air pollution and total mortality. Upton, NY: U.S. Department of Energy, Brookhaven National Laboratory; report no. BNL-52122.

Lippmann, M. (1985) Airborne acidity: estimates of exposure and human health effects. Environ. Health Perspect. 63: 63-70.

Lippmann, M.; Ito, K. (1995) Separating the effects of temperature and season on daily mortality from those of air pollution in London: 1965-1972. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 85-97.

Lippmann, M.; Thurston, G. (1996) Sulfate concentrations as an indicator of ambient particulate matter air pollution for health risk calculations. J. Exposure Anal. Environ. Epidemiol.: accepted.

Lippmann, M.; Lioy, P. J.; Leikauf, G.; Green, K. B.; Baxter, D.; Morandi, M.; Pasternack, B. S.; Fife, D.; Speizer, F. E. (1983) Effects of ozone on the pulmonary function of children. In: Lee, S. D.; Mustafa, M. G.; Mehlman, M. A., eds. International symposium on the biomedical effects of ozone and related photochemical oxidants; March 1982; Pinehurst, NC. Princeton, NJ: Princeton Scientific Publishers, Inc.; pp. 423-446. (Advances in modern environmental toxicology: v. 5).

Lunn, J. E.; Knowelden, J.; Handyside, A. J. (1967) Patterns of respiratory illness in Sheffield infant schoolchildren. Br. J. Prev. Soc. Med. 21: 7-16.

Lunn, J. E.; Knowelden, J.; Roe, J. W. (1970) Patterns of respiratory illness in Sheffield junior schoolchildren: a follow-up study. Br. J. Prev. Soc. Med. 24: 223-228.

Lyon, J. L.; Mori, M.; Gao, R. (1995) Is there a causal association between excess mortality and exposure to PM-10 air pollution? Additional analyses by location, year, season and cause of death. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 603-614.

Mackenbach, J. P.; Looman, C. W. N.; Kunst, A. E. (1993) Air pollution, lagged effects of temperature, and mortality: The Netherlands 1979-87. J. Epidemiol. Commun. Health 47: 121-126.

Martin, A. E. (1964) Mortality and morbidity statistics and air pollution. Proc. R. Soc. Med. 57: 969-975.

Martin, A. E.; Bradley, W. H. (1960) Mortality, fog and atmospheric pollution: an investigation during the winter of 1958-59. Mon. Bull. Minist. Health Public Health Lab. Serv. (GB) 19: 56-73.

Martinez, F. D.; Morgan, W. J.; Wright, A. L.; Holberg, C. J.; Taussig, L. M. (1988) Diminished lung function as a predisposing factor for wheezing respiratory illness in infants. N. Engl. J. Med. 319: 1112-1117.

Martinez, F. D.; Taussig, L. M.; Morgan, W. J. (1990) Infants with upper respiratory illnesses have significant reductions in maximal expiratory flow. Pediatr. Pulmonol. 9: 91-95.

Martinez, F. D.; Morgan, W. J.; Wright, A. L.; Holberg, C.; Taussig, L. M.; Group Health Medical Associates. (1991) Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Am. Rev. Respir. Dis. 143: 312-316.

Martinez, F. D.; Wright, A. L.; Taussig, L. M.; Holberg, C. J.; Halonen, M.; Morgan, W. J.; Group Health Medical Associates. (1995) Asthma and wheezing in the first six years of life. N. Engl. J. Med. 332: 133-138.

Mazumdar, S.; Sussman, N. (1983) Relationships of air pollution to health: results from the Pittsburgh study. Arch. Environ. Health 38: 17-24.

Mazumdar, S.; Schimmel, H.; Higgins, I. (1981) Daily mortality, smoke and SO_2 in London, England 1959 to 1972. In: Frederick, E. R., ed. A specialty conference on: the proposed SO_x and particulate standard; September 1980; Atlanta, GA. Pittsburgh, PA: Air Pollution Control Association; pp. 219-239.

Mazumdar, S.; Schimmel, H.; Higgins, I. T. T. (1982) Relation of daily mortality to air pollution: an analysis of 14 London winters, 1958/59-1971/72. Arch. Environ. Health 37: 213-220.

McConnochie, K. M.; Hall, C. B.; Barker, W. H. (1988) Lower respiratory tract illness in the first two years of life: epidemiologic patterns and costs in a suburban pediatric practice. Am. J. Public Health 78: 34-39.

McCullagh, P.; Nelder, J. A. (1983) Generalized linear models. New York, NY: Chapman and Hall. (Monographs on statistics and applied probability).

McCullagh, P.; Nelder, J. A. (1989) Generalized linear models. 2nd ed. London, United Kingdom: Chapman and Hall.

McPherson, K.; Wennberg, J. E.; Hovind, O. B.; Clifford, P. (1982) Small-area variations in the use of common surgical procedures: an international comparison of New England, England, and Norway. N. Engl. J. Med. 307: 1310-1314.

Mendelsohn, R.; Orcutt, G. (1979) An empirical analysis of air pollution dose-response curves. J. Environ. Econ. Manage. 6: 85-106.

Mickey, R. M.; Greenland, S. (1989) The impact of confounder selection criteria on effect estimation. Am. J. Epidemiol. 129: 125-137, 1066.

Moolgavkar, S. H. (1994) Air pollution and mortality [letter]. N. Engl. J. Med. 330: 1237-1238.

Moolgavkar, S. H.; Luebeck, E. G.; Hall, T. A.; Anderson, E. L. (1995a) Particulate air pollution, sulfur dioxide, and daily mortality: a reanalysis of the Steubenville data. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 35-44.

Moolgavkar, S. H.; Luebeck, E. G.; Hall, T. A.; Anderson, E. L. (1995b) Air pollution and daily mortality in Philadelphia. Epidemiology 6: 476-484.

Morris, S. C.; Shapiro, M. A.; Waller, J. H. (1976) Adult mortality in two communities with widely different air pollution levels. Arch. Environ. Health 31: 248-254.

Moshkovitz, Y.; Sclarovsky, S.; Behar, S.; Reicher-Reiss, H.; Kaplinsky, E.; Goldbourt, U.; SPRINT Study Group. (1993) Infarct site-related mortality in patients with recurrent myocardial infarction. Am. J. Med. 94: 388-394.

Murphy, T. F.; Henderson, F. W.; Clyde, W. A., Jr.; Collier, A. M.; Denny, F. W. (1981) Pneumonia: an eleven-year study in a pediatric practice. Am. J. Epidemiol. 113: 12-21.

National Center for Health Statistics. (1993a) Advance report of final mortality statistics, 1991. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. (Monthly vital statistics report: v. 42, no. 2, suppl.).

National Center for Health Statistics. (1993b) National Hospital Discharge Survey: annual summary, 1991. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; DHHS publication no. (PHS)93-1775. (Series 13, data from the National Health Survey: no. 114).

National Center for Health Statistics. (1994a) Mortality surveillance system charts. Mon. Vital Stat. Rep. 43(5): 6-7.

National Center for Health Statistics. (1994b) Detailed diagnoses and procedures, National Hospital Discharge Survey, 1992. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; DHHS publication no. (PHS) 94-1779. (Series 13, data from the National Health Survey: no. 118).

National Center for Health Statistics. (1994c) Current estimates from the National Health Interview Survey, 1992. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; DHHS publication no. (PHS) 94-1517. (Data from the National Health Survey: series 10, no. 189).

National Institutes of Health. (1991) Guidelines for the diagnosis and management of asthma. Bethesda, MD: U.S. Department of Health and Human Services, National Heart, Lung, and Blood Institute, National Asthma Education Program; publication no. 91-3042.

Neas, L. M.; Dockery, D. W.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr.; Speizer, F. E. (1994) Concentration of indoor particulate matter as a determinant of respiratory health in children. Am. J. Epidemiol. 139: 1088-1099.

Neas, L. M.; Dockery, D. W.; Koutrakis, P.; Tollerud, D. J.; Speizer, F. E. (1995) The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. Am. J. Epidemiol. 141: 111-122.

Örtqvist, Å.; Hedlund, J.; Grillner, L.; Jalonen, E.; Kallings, I.; Leinonen, M.; Kalin, M. (1990) Aetiology, outcome and prognostic factors in community-acquired pneumonia requiring hospitalization. Eur. Respir. J. 3: 1105-1113.

Osborne, M. L.; Vollmer, W. M.; Buist, A. S. (1992) Diagnostic accuracy of asthma within a health maintenance organization. J. Clin. Epidemiol. 45: 403-411.

Ostro, B. D. (1983) The effects of air pollution on work loss and morbidity. J. Environ. Econ. Manage. 10: 371-382.

Ostro, B. (1984) A search for a threshold in the relationship of air pollution to mortality: a reanalysis of data on London winters. Environ. Health Perspect. 58: 397-399.

Ostro, B. D. (1987) Air pollution and morbidity revisited: a specification test. J. Environ. Econ. Manage. 14: 87-98.

Ostro, B. (1993) The association of air pollution and mortality: examining the case for inference. Arch. Environ. Health 48: 336-342.

Ostro, B. D.; Rothschild, S. (1989) Air pollution and acute respiratory morbidity: an observational study of multiple pollutants. Environ. Res. 50: 238-247.

Ostro, B.; Lipsett, M.; Wiener, M.; Selner, J. C. (1989) A panel study of the effect of acid aerosols on asthmatics. Presented at: 82nd annual meeting and exhibition of the Air and Waste Management Association; June; Anaheim, CA. Pittsburgh, PA: Air & Waste Management Association; paper no. 89-94.1.

Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols. Am. J. Public Health 81: 694-702.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Krupnick, A.; Harrington, W. (1993) Air pollution and respiratory morbidity among adults in Southern California. Am. J. Epidemiol. 137: 691-700.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 711-722.

Ostro, B.; Sanchez, J. M.; Aranda, C.; Eskeland, G. S. (1996) Air pollution and mortality: results from a study of Santiago, Chile. In: Lippmann, M., ed. Papers from the ISEA-ISEE annual meeting; September 1994; Research Triangle Park, NC. J. Exposure Anal. Environ. Epidemiol.: in press.

Özkaynak, H.; Spengler, J. D. (1985) Analysis of health effects resulting from population exposures to acid precipitation precursors. Environ. Health Perspect. 63: 45-55.

Özkaynak, H.; Thurston, G. D. (1987) Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. Risk Anal. 7: 449-461.

Özkaynak, H.; Spengler, J. D.; Garsd, A.; Thurston, G. D. (1986) Assessment of population health risks resulting from exposures to airborne particles. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies, proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 1067-1080.

Özkaynak, H.; Xue, J.; Severance, P.; Burnett, R.; Raizenne, M. (1994) Associations between daily mortality, ozone, and particulate air pollution in Toronto, Canada. Presented at: Colloquium on particulate air pollution and human mortality and morbidity: program and abstracts; January; Irvine, CA. Irvine, CA: University of California Irvine, Air Pollution Health Effects Laboratory; p. P1.13; report no. 94-02.

Parcel, G. S.; Gilman, S. C.; Nader, P. R.; Bunce, H. (1979) A comparison of absentee rates of elementary schoolchildren with asthma and nonasthmatic schoolmates. Pediatrics 64: 878-881.

Perry, G. B.; Chai, H.; Dickey, D. W.; Jones, R. H.; Kinsman, R. A.; Morrill, C. G.; Spector, S. L.; Weiser, P. C. (1983) Effects of particulate air pollution on asthmatics. Am. J. Public Health 73: 50-56.

Pocock, S. J.; Shaper, A. G.; Cook, D. G.; Packham, R. F.; Lacey, R. F.; Powell, P.; Russell, P. F. (1980) British regional heart study: geographic variations in cardiovascular mortality, and the role of water quality. Br. Med. J. 280: 1243-1249.

Pönkä, A. (1991) Asthma and low level air pollution in Helsinki. Arch. Environ. Health 46: 262-270.

Pönkä, A.; Virtanen, M. (1994) Chronic bronchitis, emphysema, and low-level air pollution in Helsinki, 1987-1989. Environ. Res. 65: 207-217.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM_{10} pollution in Utah, Salt Lake, and Cache Valleys. Arch. Environ. Health 46: 90-97.

Pope, C. A., III. (1994) Particulate pollution and mortality in Utah valley. Prepared for: Critical evaluation workshop on particulate matter—mortality epidemiology studies; November; Raleigh, NC. Provo, UT: Brigham Young University.

Pope, C. A., III; Dockery, D. W. (1992) Acute health effects of PM_{10} pollution on symptomatic and asymptomatic children. Am. Rev. Respir. Dis. 145: 1123-1128.

Pope, C. A., III; Kalkstein, L. S. (1996) Synoptic weather modeling and estimates of the exposure-response relationship between daily mortality and particulate air pollution. Environ. Health Perspect. 104: in press.

Pope, C. A., III; Kanner, R. E. (1993) Acute effects of PM_{10} pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 147: 1336-1340.

Pope, C. A., III; Dockery, D. W.; Spengler, J. D.; Raizenne, M. E. (1991) Respiratory health and PM_{10} pollution: a daily time series analysis. Am. Rev. Respir. Dis. 144: 668-674.

Pope, C. A., III; Schwartz, J.; Ransom, M. R. (1992) Daily mortality and PM_{10} pollution in Utah valley. Arch. Environ. Health 47: 211-217.

Pope, C. A., III; Dockery, D. W.; Schwartz, J. (1995a) Review of epidemiological evidence of health effects of particulate air pollution. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 1-18.

Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr. (1995b) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Respir. Crit. Care Med. 151: 669-674.

Quackenboss, J. J.; Krzyzanowski, M.; Lebowitz, M. D. (1991) Exposure assessment approaches to evaluate respiratory health effects of particulate matter and nitrogen dioxide. J. Exposure Anal. Environ. Epidemiol. 1: 83-107.

Quandt, R. E. (1958) The estimation of the parameters of a linear regression system obeying two separate regimes. J. Am. Stat. Assoc. 53: 873-880.

Queiros, M.; Bonito-Vitor, A.; Costa-Pereira, A.; Costa Maia, J. (1990) Childhood asthma and outdoor air pollution in Oporto area. Allergol. Immunopathol. 18: 291-295.

Raizenne, M.; Burnett, R.; Stern, B.; Meranger, J. C. (1987) Transported air pollutants and respiratory health in two Canadian communities. Chest 91: 314.

Raizenne, M. E.; Burnett, R. T.; Stern, B.; Franklin, C. A.; Spengler, J. D. (1989) Acute lung function responses to ambient acid aerosol exposures in children. Environ. Health Perspect. 79: 179-185.

Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. Environ. Health Perspect.: accepted.

Ramlow, J. M.; Kuller, L. H. (1990) Effects of the summer heat wave of 1988 on daily mortality in Allegheny County, PA. Public Health Rep. 105: 283-289.

Ransom, M. R.; Pope, C. A., III. (1992) Elementary school absences and PM_{10} pollution in Utah Valley. Environ. Res. 58: 204-219.

Ricci, P. F.; Wyzga, R. E. (1983) An overview of cross-sectional studies of mortality and air pollution and related statistical issues. Environ. Int. 9: 177-194.

Richardson, S. L.; Renz, K. K.; Vogel, T. T.; Graham, J. E., Jr.; Kaufman, J. (1991) Small area analysis shows differences in utilization. Qual. Assur. Util. Rev. 6: 91-94.

Rieves, R. D.; Bass, D.; Carter, R. R.; Griffith, J. E.; Norman, J. R. (1993) Severe COPD and acute respiratory failure: correlates for survival at the time of tracheal intubation. Chest 104: 854-860.

Robertson, J. M.; Ingalls, T. H. (1989) A case-control study of circulatory, malignant, and respiratory morbidity in carbon black workers in the United States. Am. Ind. Hyg. Assoc. J. 50: 510-515.

Roemer, W.; Hoek, G.; Brunekreef, B. (1993) Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. Am. Rev. Respir. Dis. 147: 118-124.

Rogot, E.; Sorlie, P. D.; Johnson, N. J.; Schmitt, C. (1992) A mortality study of 1.3 million persons by demographic, social, and economic factors: 1979-1985 follow-up. Bethesda, MD: National Institutes of Health; NIH publication no. 92-3297.

Rothman, K. J. (1986) Modern epidemiology. Boston, MA: Little, Brown and Co.

Rothman, N.; Ford, D. P.; Baser, M. E.; Hansen, J. A.; O'Toole, T.; Tockman, M. S.; Strickland, P. T. (1991) Pulmonary function and respiratory symptoms in wildland firefighters. J. Occup. Med. 33: 1163-1167.

Saldiva, P. H. N.; Lichtenfels, A. J. F. C.; Paiva, P. S. O.; Barone, I. A.; Martins, M. A.; Massad, E.; Pereira, J. C. R.; Xavier, V. P.; Singer, J. M.; Böhm, G. M. (1994) Association between air pollution and mortality due to respiratory diseases in children in São Paulo, Brazil: a preliminary report. Environ. Res. 65: 218-225.

Saldiva, P. H. N.; Pope, C. A., III; Schwartz, J.; Dockery, D. W.; Lichtenfels, A. J.; Salge, J. M.; Barone, I.; Bohm, G. M. (1995) Air pollution and mortality in elderly people: a time-series study in São Paulo, Brazil. Arch. Environ. Health 50: 159-163.

Samet, J. M.; Utell, M. J. (1990) The risk of nitrogen dioxide: what have we learned from epidemiological and clinical studies? Toxicol. Ind. Health 6: 247-262.

Samet, J. M.; Tager, I. B.; Speizer, F. E. (1983) The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. Am. Rev. Respir. Dis. 127: 508-523.

Samet, J. M.; Zeger, S. L.; Berhane, K. (1995) The association of mortality and particulate air pollution. In: Particulate air pollution and daily mortality: replication and validation of selected studies, the phase I report of the particle epidemiology evaluation project [preprint]. Cambridge, MA: Health Effects Institute; pp. 1-104.

Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J. (1996a) Air pollution and mortality in Philadelphia, 1974-1988, report to the Health Effects Institute on phase IB: Particle Epidemiology Evaluation Project. Cambridge, MA: Health Effects Institute; accepted.

Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J.; Kalkstein, L. S. (1996b) Weather, air pollution and mortality in Philadelphia, 1973-1980, report to the Health Effects Institute on phase IB, Particle Epidemiology Evaluation Project. Cambridge, MA: Health Effects Institute; review draft.

Sandvik, L.; Erikssen, J.; Thaulow, E.; Erikssen, G.; Mundal, R.; Rodahl, K. (1993) Physical fitness as a predictor of mortality among healthy, middle-aged Norwegian men. N. Engl. J. Med. 328: 533-537.

Schenker, M. B.; Speizer, F. E.; Samet, J. M.; Gruhl, J.; Batterman, S. (1983) Health effects of air pollution due to coal combustion in the Chestnut Ridge region of Pennsylvania: results of cross-sectional analysis in adults. Arch. Environ. Health 38: 325-330.

Schimmel, H. (1978) Evidence for possible acute health effects of ambient air pollution from time series analysis: methodological questions and some new results based on New York City daily mortality, 1963-1976. Bull. N. Y. Acad. Med. 54: 1052-1108.

Schrenk, H. H.; Heimann, H.; Clayton, G. D.; Gafafer, W. M.; Wexler, H. (1949) Air pollution in Donora, PA. Epidemiology of the unusual smog episode of October 1948: preliminary report. Washington, DC: Public Health Service; Public Health Service bulletin no. 306.

Schwartz, J. (1989) Lung function and chronic exposure to air pollution: a cross-sectional analysis of NHANES II. Environ. Res. 50: 309-321.

Schwartz, J. (1991a) Particulate air pollution and daily mortality in Detroit. Environ. Res. 56: 204-213.

Schwartz, J. (1991b) The first author replies [letter re Fleisher and Nayeri (1991)]. Am. J. Epidemiol. 133: 632-633.

Schwartz, J. (1992) Particulate air pollution and daily mortality: a synthesis. Public Health Rev. 19: 39-60.

Schwartz, J. (1993a) Air pollution and daily mortality in Birmingham, Alabama. Am. J. Epidemiol. 137: 1136-1147.

Schwartz, J. (1993b) Particulate air pollution and chronic respiratory disease. Environ. Res. 62: 7-13.

Schwartz, J. (1994a) Total suspended particulate matter and daily mortality in Cincinnati, Ohio. Environ. Health Perspect. 102: 186-189.

Schwartz, J. (1994b) Air pollution and daily mortality: a review and meta analysis. Environ. Res. 64: 36-52.

Schwartz, J. (1994c) What are people dying of on high air pollution days? Environ. Res. 64: 26-35.

Schwartz, J. (1994d) Air pollution and hospital admissions for the elderly in Detroit, Michigan. Am. J. Respir. Crit. Care Med. 150: 648-655.

Schwartz, J. (1994e) Air pollution and hospital admissions for the elderly in Birmingham, Alabama. Am. J. Epidemiol. 139: 589-598.

Schwartz, J. (1994f) PM_{10}, ozone, and hospital admissions for the elderly in Minneapolis, MN. Arch. Environ. Health 49: 366-374.

Schwartz, J. (1994g) Nonparametric smoothing in the analysis of air pollution and respiratory illness. Can. J. Stat. 22: 1-17.

Schwartz, J. (1994h) The use of generalized additive models in epidemiology. In: IBC'94, XVIIth International Biometric Society conference proceedings, volume 1: invited papers; August; Hamilton, Ontario, Canada. Hamilton, Ontario, Canada: McMaster University, Department of Mathematics and Statistics, IBC'94 Local Organizing Committee; pp. 55-80.

Schwartz, J. (1995a) Short term fluctuations in air pollution and hospital admissions of the elderly for respiratory disease. Thorax 50: 531-538.

Schwartz, J. (1995b) Health effects of air pollution from traffic: ozone and particulate matter. In: Fletcher, T., ed. Health at the crossroads: transportation policy and urban health, proceedings of the fifth annual public health forum of

the London School of Hygiene and Tropical Medicine; April; London, United Kingdom. New York, NY: John Wiley & Sons, Inc.; in preparation.

Schwartz, J. (1996) Air pollution and hospital admissions for respiratory disease. Epidemiology 7: 20-28.

Schwartz, J.; Dockery, D. W. (1992a) Increased mortality in Philadelphia associated with daily air pollution concentrations. Am. Rev. Respir. Dis. 145: 600-604.

Schwartz, J.; Dockery, D. W. (1992b) Particulate air pollution and daily mortality in Steubenville, Ohio. Am. J. Epidemiol. 135: 12-19.

Schwartz, J.; Marcus, A. H. (1986) Statistical reanalyses of data relating mortality to air pollution during London winters 1958-1972. Washington, DC: U.S. Environmental Protection Agency, Office of Policy, Planning and Evaluation.

Schwartz, J.; Marcus, A. (1990) Mortality and air pollution in London: a time series analysis. Am. J. Epidemiol. 131: 185-194.

Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.

Schwartz, J.; Spix, C.; Wichmann, H. E.; Malin, E. (1991a) Air pollution and acute respiratory illness in five German communities. Environ. Res. 56: 1-14.

Schwartz, J.; Wypij, D.; Dockery, D.; Ware, J.; Zeger, S.; Spengler, J.; Ferris, B., Jr. (1991b) Daily diaries of respiratory symptoms and air pollution: methodological issues and results. Environ. Health Perspect. 90: 181-187.

Schwartz, J.; Slater, D.; Larson, T. V.; Pierson, W. E.; Koenig, J. Q. (1993) Particulate air pollution and hospital emergency room visits for asthma in Seattle. Am. Rev. Respir. Dis. 147: 826-831.

Schwartz, J.; Dockery, D. W.; Neas, L. M.; Wypij, D.; Ware, J. H.; Spengler, J. D.; Koutrakis, P.; Speizer, F. E.; Ferris, B. G., Jr. (1994) Acute effects of summer air pollution on respiratory symptom reporting in children. Am. J. Respir. Crit. Care Med. 150: 1234-1242.

Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996a) Is daily mortality associated specifically with fine particles? J. Air Waste Manage. Assoc.: accepted.

Schwartz, J.; Spix, C.; Touloumi, G.; Bacharova, L.; Barumamdzadeh, T.; Le Tertre, A.; Piekarksi, T.; Ponce de Leon, A.; Ponka, A.; Rossi, G.; Saez, M.; Shouten, J. P. (1996b) Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. J. Epidemiol. Commun. Health: in press.

Schwarz, G. (1978) Estimating the dimension of a model. Ann. Stat. 6: 461-464.

Shapiro, S. (1994) Meta-analysis/shmeta-analysis. Am. J. Epidemiol. 140: 771-778.

Shumway, R. H.; Tai, R. Y.; Tai, L. P.; Pawitan, Y. (1983) Statistical analysis of daily London mortality and associated weather and pollution effects. Sacramento, CA: California Air Resources Board; contract no. A1-154-33.

Shumway, R. H.; Azari, A. S.; Pawitan, Y. (1988) Modeling mortality fluctuations in Los Angeles as functions of pollution and weather effects. Environ. Res. 45: 224-241.

Shusterman, D.; Kaplan, J. Z.; Canabarro, C. (1993) Immediate health effects of an urban wildfire. West. J. Med. 158: 133-138.

Siegel, P. Z.; Frazier, E. L.; Mariolis, P.; Brackbill, R. M.; Smith, C. (1993) Behavioral risk factor surveillance, 1991: monitoring progress toward the nation's year 2000 health objectives. Morb. Mortal. Wkly Rep. 42: 1-20.

Silverman, F.; Hosein, H. R.; Corey, P.; Holton, S.; Tarlo, S. M. (1992) Effects of particulate matter exposure and medication use on asthmatics. Arch. Environ. Health 47: 51-56.

Skobeloff, E. M.; Spivey, W. H.; St. Clair, S. S.; Schoffstall, J. M. (1992) The influence of age and sex on asthma admissions. JAMA J. Am. Med. Assoc. 268: 3437-3440.

Smith, V. K. (1975) Mortality-air pollution relationships: a comment. JASA J. Am. Stat. Assoc. 70: 341-343.

Sorlie, P. D.; Rogot, E. (1990) Mortality by employment status in the National Longitudinal Mortality Study. Am. J. Epidemiol. 132: 983-992.

Speizer, F. E. (1989) Studies of acid aerosols in six cities and in a new multi-city investigation: design issues. Environ. Health Perspect. 79: 61-67.

Spektor, D. M.; Yen, B. M.; Lippmann, M. (1989) Effect of concentration and cumulative exposure of inhaled sulfuric acid on tracheobronchial particle clearance in healthy humans. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 167-172.

Spektor, D. M.; Lippmann, M.; Lioy, P. J.; Thurston, G. D.; Citak, K.; James, D. J.; Bock, N.; Speizer, F. E.; Hayes, C. (1988) Effects of ambient ozone on respiratory function in active, normal children. Am. Rev. Respir. Dis. 137: 313-320.

Spektor, D. M.; Hofmeister, V. A.; Artaxo, P.; Brague, J. A. P.; Echelar, F.; Nogueira, D. P.; Hayes, C.; Thurston, G. D.; Lippmann, M. (1991) Effects of heavy industrial pollution on respiratory function in the children of Cubatao, Brazil: a preliminary report. Environ. Health Perspect. 94: 51-54.

Spengler, J. D.; Allen, G. A.; Foster, S.; Severance, P.; Ferris, B., Jr. (1986) Sulfuric acid and sulfate aerosol events in two U. S. cities. In: Lee, S. D.; Schneider, T.; Grant, L. D.; Verkerk, P. J., eds. Aerosols: research, risk assessment and control strategies - proceedings of the second U.S.-Dutch international symposium; May 1985; Williamsburg, VA. Chelsea, MI: Lewis Publishers, Inc.; pp. 107-120.

Spengler, J. D.; Keeler, G. J.; Koutrakis, P.; Ryan, P. B.; Raizenne, M.; Franklin, C. A. (1989) Exposures to acidic aerosols. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 43-51.

Spengler, J. D.; Koutrakis, P.; Dockery, D. W.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: air pollution exposures. Environ. Health Perspect.: in press.

Spix, C.; Heinrich, J.; Dockery, D.; Schwartz, J.; Völksch, G.; Schwinkowski, K.; Cöllen, C.; Wichmann, H. E. (1993) Air pollution and daily mortality in Erfurt, East Germany, 1980-1989. Environ. Health Perspect. 101: 518-526.

Spix, C.; Heinrich, J.; Dockery, D.; Schwartz, J.; Volksch, G.; Schwinkowski, K.; Collen, C.; Wichmann, H. E. (1994) Summary of the analysis and reanalysis corresponding to the publication Air pollution and daily mortality in Erfurt, East Germany 1980-1989. Summary report for: Critical evaluation workshop on particulate matter—mortality epidemiology studies; November; Raleigh, NC. Wuppertal, Germany: Bergische Universitat-Gesamthochschule Wuppertal.

Stern, B.; Jones, L.; Raizenne, M.; Burnett, R.; Meranger, J. C.; Franklin, C. A. (1989) Respiratory health effects associated with ambient sulfates and ozone in two rural Canadian communities. Environ. Res. 49: 20-39.

Stern, B. R.; Raizenne, M. E.; Burnett, R. T.; Jones, L.; Kearney, J.; Franklin, C. A. (1994) Air pollution and childhood respiratory health: exposure to sulfate and ozone in 10 Canadian rural communities. Environ. Res. 66: 125-142.

Stokinger, H. E. (1972) Concepts of thresholds in standards setting: an analysis of the concept and its application to industrial air limits (TLVs). Arch. Environ. Health 25: 153-157.

Storr, J.; Lenney, W. (1989) School holidays and admissions with asthma. Arch. Dis. Child. 64: 103-107.

Studnicka, M. J.; Frischer, T.; Meinert, R.; Studnicka-Benke, A.; Hajek, K.; Spengler, J. D.; Neumann, M. G. (1995) Acidic particles and lung function in children: a summer camp study in the Austrian Alps. Am. J. Respir. Crit. Care Med. 151: 423-430.

Styer, P.; McMillan, N.; Gao, F.; Davis, J.; Sacks, J. (1995) The effect of airborne particulate matter on daily death counts. Environ. Health Perspect. 103: 490-497.

Suh, H. H.; Allen, G. A.; Koutrakis, P.; Burton, R. M. (1995) Spatial variation in acidic sulfate and ammonia concentrations within metropolitan Philadelphia. J. Air Waste Manage. Assoc. 45: 442-452.

Sunyer, J.; Antó, J. M.; Murillo, C.; Sáez, M. (1991) Effects of urban air pollution on emergency room admissions for chronic obstructive pulmonary disease. Am. J. Epidemiol. 134: 277-286.

Sunyer, J.; Sáez, M.; Murillo, C.; Castellsague, J.; Martínez, F.; Antó, J. M. (1993) Air pollution and emergency room admissions for chronic obstructive pulmonary disease: a 5-year study. Am. J. Epidemiol. 137: 701-705.

Tager, I. B.; Segal, M. R.; Speizer, F. E.; Weiss, S. T. (1988) The natural history of forced expiratory volumes: effect of cigarette smoking and respiratory symptoms. Am. Rev. Respir. Dis. 138: 837-849.

Tager, I. B.; Hanrahan, J. P.; Tosteson, T. D.; Castile, R. G.; Brown, R. W.; Weiss, S. T.; Speizer, F. E. (1993) Lung function, pre- and post-natal smoke exposure, and wheezing in the first year of life. Am. Rev. Respir. Dis. 147: 811-817.

Tashkin, D. P.; Detels, R.; Simmons, M.; Liu, H.; Coulson, A. H.; Sayre, J.; Rokaw, S. (1994) The UCLA population studies of chronic obstructive respiratory disease: XI. impact of air pollution and smoking on annual change in forced expiratory volume in one second. Am. J. Respir. Crit. Care Med. 149: 1209-1217.

Thibodeau, L. A.; Reed, R. B.; Bishop, Y. M. M.; Kammerman, L. A. (1980) Air pollution and human health: a review and reanalysis. Environ. Health Perspect. 34: 165-183.

Thomas, K. W.; Pellizzari, E. D.; Clayton, C. A.; Whitaker, D. A.; Shores, R. C.; Spengler, J.; Özkaynak, H.; Froehlich, S. E.; Wallace, L. A. (1993) Particle total exposure assessment methodology (PTEAM) 1990 study: method performance and data quality for personal, indoor, and outdoor monitoring. J. Exposure Anal. Environ. Epidemiol. 3: 203-226.

Thomson, M.; Philion, J. (1991) Children's respiratory hospitalizations and air pollution. Can. J. Public Health 82: 203-204.

Thurston, G. D.; Kinney, P. L. (1995) Air pollution epidemiology: considerations in time-series modeling. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 71-83.

Thurston, G. D.; Özkaynak, H. (1992) Air pollution and mortality [letter]. Science (Washington, DC) 255: 382-383.

Thurston, G. D.; Ito, K.; Lippmann, M.; Hayes, C. (1989) Reexamination of London, England, mortality in relation to exposure to acidic aerosols during 1963-1972 winters. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 73-82.

Thurston, G. D.; Ito, K.; Kinney, P. L.; Lippmann, M. (1992) A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: results for 1988 and 1989 summers. J. Exposure Anal. Environ. Epidemiol. 2: 429-450.

Thurston, G. D.; Gorczynski, J. E., Jr.; Currie, J. H.; He, D.; Ito, K.; Hipfner, J.; Waldman, J.; Lioy, P. J.; Lippmann, M. (1994a) The nature and origins of acid summer haze air pollution in metropolitan Toronto, Ontario. Environ. Res. 65: 254-270.

Thurston, G. D.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994b) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ. Res. 65: 271-290.

Touloumi, G.; Pocock, S. J.; Katsouyanni, K.; Trichopoulos, D. (1994) Short-term effects of air pollution on daily mortality in Athens: a time-series analysis. Int. J. Epidemiol. 23: 957-967.

Tromp, S. W. (1980) Biometeorology: the impact of weather and climate on humans and their environment (animals and plants). London, United Kingdom: Heyden.

Tseng, R. Y. M.; Li, C. K.; Spinks, J. A. (1992) Particulate air pollution and hospitalization for asthma. Ann. Allergy 68: 425-432.

Tzonou, A.; Maragoudakis, G.; Trichopoulos, D.; Zavitsanos, X.; Dimopoulou, I.; Toupadaki, N.; Kremastinou, J. (1992) Urban living, tobacco smoking, and chronic obstructive pulmonary disease: a study in Athens. Epidemiology 3: 57-60.

U.S. Centers for Disease Control. (1994) Populations at risk from particulate air pollution—United States, 1992. Morb. Mortal. Wkly. Rep. 43: 290-293.

U.S. Centers for Disease Control. (1995) Asthma—United States, 1982-1992. Morb. Mortal. Wkly. Rep. 43: 952-955.

U.S. Department of Health, Education, and Welfare. (1964) Smoking and health: report of the Advisory Committee to the Surgeon General of the Public Health Service. Washington, DC: Public Health Service; p. 60.

U.S. Environmental Protection Agency. (1982a) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

U.S. Environmental Protection Agency. (1982b) Review of the national ambient air quality standards for particulate matter: assessment of scientific and technical information. Research Triangle Park, NC: Office of Air Quality Planning and Standards, Strategies and Air Standards Division; report no. EPA-450/5-82-001. Available from: NTIS, Springfield, VA; PB82-177874.

U.S. Environmental Protection Agency. (1986a) Second addendum to air quality criteria for particulate matter and sulfur oxides (1982): assessment of newly available health effects information. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-86-020F. Available from: NTIS, Springfield, VA; PB87-176574.

U.S. Environmental Protection Agency. (1986b) Review of the national ambient air quality standards for particulate matter: updated assessment of scientific and technical information, addendum to the 1982 OAQPS staff paper. Research Triangle Park, NC: Office of Air Quality Planning and Standards, Strategies and Air Standards Division; report no. EPA/450/05-86/012. Available from: NTIS, Springfield, VA; PB87-176871/XAB.

U.S. Environmental Protection Agency. (1986c) Air quality criteria for ozone and other photochemical oxidants. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report nos. EPA-600/8-84-020aF-eF. 5v. Available from: NTIS, Springfield, VA; PB87-142949.

U.S. Environmental Protection Agency. (1989) An acid aerosols issue paper: health effects and aerometrics. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-88-005F. Available from: NTIS, Springfield, VA; PB91-125864.

U.S. Environmental Protection Agency. (1992) Respiratory health effects of passive smoking: lung cancer and other disorders. Washington, DC: Office of Research and Development, Office of Health and Environmental Assessment; EPA report no. EPA/600/6-90/006F. Available from: NTIS, Springfield, VA; PB93-134419/XAB.

U.S. Environmental Protection Agency. (1993) Air quality criteria for oxides of nitrogen. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA/600/8-91/049aF-cF. 3v. Available from: NTIS, Springfield, VA; PB95-124533, PB95-124525, PB95-124517.

U.S. Environmental Protection Agency. (1996) Air quality criteria for ozone and related photochemical oxidants [draft final]. Research Triangle Park, NC: National Center for Environmental Assessment-RTP Office; EPA report nos. EPA/600/AP-93/004aF-cF. 3v.

U.S. Senate. (1968) Air quality criteria staff report. Washington, DC: Committee on Public Works; serial no. 94-411.

Ulm, K. (1991) A statistical method for assessing a threshold in epidemiological studies. Stat. Med. 10: 341-349.

United Kingdom Ministry of Health. (1954) Mortality and morbidity during the London fog of December 1952. London, United Kingdom: Her Majesty's Stationery Office. (Reports on public health and medical subjects no. 95).

Utell, M. J.; Morrow, P. E.; Speers, D. M.; Darling, J.; Hyde, R. W. (1983) Airway responses to sulfate and sulfuric acid aerosols in asthmatics: an exposure-response relationship. Am. Rev. Respir. Dis. 128: 444-450.

Vedal, S.; Schenker, M. B.; Samet, J. M.; Speizer, F. E. (1984) Risk factors for childhood respiratory disease: analysis of pulmonary function. Am. Rev. Respir. Dis. 130: 187-192.

Waldron, H. A. (1974) The blood lead threshold. Arch. Environ. Health 29: 271-273.

Waller, R. E. (1963) Acid droplets in town air. Int. J. Air Water Pollut. 7: 773-778.

Waller, R. E. (1971) Air pollution and community health. J. R. Coll. Physicians (London) 5: 362-368.

Waller, R. E.; Lawther, P. J. (1957) Further observations on London fog. Br. Med. J. 4: 1473-1475.

Walters, S.; Griffiths, R. K.; Ayres, J. G. (1994) Temporal association between hospital admissions for asthma in Birmingham and ambient levels of sulphur dioxide and smoke. Thorax 49: 133-140.

Wang, X.; Dockery, D. W.; Wypij, D.; Fay, M. E.; Ferris, B. G., Jr. (1993a) Pulmonary function between 6 and 18 years of age. Pediatr. Pulmonol. 15: 75-88.

Wang, X.; Dockery, D. W.; Wypij, D.; Gold, D. R.; Speizer, F. E.; Ware, J. H.; Ferris, B. G., Jr. (1993b) Pulmonary function growth velocity in children 6 to 18 years of age. Am. Rev. Respir. Dis. 148: 1502-1508.

Ware, J. H.; Thibodeau, L. A.; Speizer, F. E.; Colome, S.; Ferris, B. G., Jr. (1981) Assessment of the health effects of atmospheric sulfur oxides and particulate matter: evidence from observational studies. Environ. Health Perspect. 41: 255-276.

Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.

Weiss, K. B. (1990) Seasonal trends in US asthma hospitalizations and mortality. JAMA J. Am. Med. Assoc. 263: 2323-2328.

Weiss, S. M.; Hudson, L. D. (1994) Outcome from respiratory failure. Crit. Care Clin. 10: 197-215.

Weitzman, M. (1986) School absence rates as outcome measures in studies of children with chronic illness. J. Chronic Dis. 39: 799-808.

Weitzman, M.; Klerman, L. V.; Alpert, J. J.; Lamb, G. A.; Kayne, H.; Rose, L. (1986) Factors associated with excessive school absence. Pediatrician 13: 74-80.

Wennberg, J. E. (1987) Population illness rates do not explain population hospitalization rates: a comment on Mark Blumberg's thesis that morbidity adjusters are needed to interpret small area variations. Med. Care 25: 354-359.

Wennberg, J. E.; McPherson, K.; Caper, P. (1984) Will payment based on diagnosis-related groups control hospital costs? N. Engl. J. Med. 311: 295-300.

Westfall, P. H.; Young, S. S. (1993) Resampling-based multiple testing: examples and methods for *p*-value adjustment. New York, NY: John Wiley & Sons, Inc.

White, M. C.; Etzel, R. A.; Wilcox, W. D.; Lloyd, C. (1994) Exacerbations of childhood asthma and ozone pollution in Atlanta. Environ. Res. 65: 56-68.

Whittemore, A. S.; Korn, E. L. (1980) Asthma and air pollution in the Los Angeles area. Am. J. Public Health 70: 687-696.

Wichmann, H.-E.; Sugiri, D.; Islam, M. S.; Haake, D.; Roscovanu, A. (1988a) Lungenfunktion und Carboxyhämoglobin in der Smogsituation des Januar 1987 [Pulmonary function and carboxyhemoglobin during the smog episode in January 1987]. Zentralbl. Bakteriol. Mikrobiol. Hyg. Abt. 1 Orig. B 187: 31-43.

Wichmann, H.-E.; Sugiri, D.; Herold, G.; Knülle, E. (1988b) Atemwiderstandsmessungen bei Gesunden im Winterhalbjahr 1985/86 und im Januar/Februar 1987 [Measurement of airway resistance in healthy persons during the winter of 1985/86 and in January and February 1987]. Zentralbl. Bakteriol. Mikrobiol. Hyg. Ser. B 185: 509-519.

Wichmann, H. E.; Mueller, W.; Allhoff, P.; Beckmann, M.; Bocter, N.; Csicsaky, M. J.; Jung, M.; Molik, B.; Schoeneberg, G. (1989) Health effects during a smog episode in West Germany in 1985. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 89-99.

Williams, M. K. (1970) Sickness absence and ventilatory capacity of workers exposed to sulphuric acid mist. Br. J. Ind. Med. 27: 61-66.

Wilson, W. E.; Suh, H. H. (1995) Differentiating fine and coarse particles: definitions and exposure relationships relevant to epidemiological studies. In: Schmidt-Ott, A., ed. Trends in aerosol research IV: new approaches in aerosol science and technology, proceedings of the seminar; January; Gerhard Mercator University, Duisburg, Germany. Duisburg, Germany: Gerhard Mercator University of Duisburg; pp. 57-71.

Wolff, G. T.; Stroup, C. M.; Stroup, D. P. (1983) The coefficient of haze as a measure of particulate elemental carbon. J. Air Pollut. Control Assoc. 33: 746-750.

World Health Organization. (1977) Manual of the international statistical classification of diseases, injuries, and causes of death. Geneva, Switzerland: World Health Organization.

World Health Organization. (1996) Climate change and human health. Geneva, Switzerland: WHO/WMO/UNEP; in press.

Wright, A. L.; Taussig, L. M.; Ray, C. G.; Harrison, H. R.; Holberg, C. J. (1989) The Tucson children's respiratory study: II. lower respiratory tract illness in the first year of life. Am. J. Epidemiol. 129: 1232-1246.

Wyzga, R. (1978) The effect of air pollution upon mortality: a consideration of distributed lag models. JASA J. Am. Stat. Assoc. 73: 463-472.

Wyzga, R. E.; Lipfert, F. W. (1995a) Ozone and daily mortality: the ramifications of uncertainties and interactions and some initial regression results. Presented at: AWMA specialty conference on tropospheric ozone; May 1994; Orlando, FL. Pittsburgh, PA: Air & Waste Management Association; in press.

Wyzga, R. E.; Lipfert, F. W. (1995b) Temperature-pollution interactions with daily mortality in Philadelphia. In: Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; pp. 3-42. (A&WMA publication VIP-49).

Xu, Z.-Y.; Blot, W. J.; Xiao, H.-P.; Wu, A.; Feng, Y.-P.; Stone, B. J.; Sun, J.; Ershow, A. G.; Henderson, B. E.; Fraumeni, J. F., Jr. (1989) Smoking, air pollution, and the high rates of lung cancer in Shenyang, China. J. Natl. Cancer Inst. 81: 1800-1806.

Xu, X.; Dockery, D. W.; Wang, L. (1991) Effects of air pollution on adult pulmonary function. Arch. Environ. Health 46: 198-206.

Xu, X.; Gao, J.; Dockery, D. W.; Chen, Y. (1994) Air pollution and daily mortality in residential areas of Beijing, China. Arch. Environ. Health 49: 216-222.

Yano, E.; Yokoyama, Y.; Higashi, H.; Nishii, S.; Maeda, K.; Koizumi, A. (1990) Health effects of volcanic ash: a repeat study. Arch. Environ. Health 45: 367-373.

Zeger, S. L.; Liang, K.-Y. (1986) Longitudinal data analysis for discrete and continuous outcomes. Biometrics 42: 121-130.

13. INTEGRATIVE SYNTHESIS OF KEY POINTS: PM EXPOSURE, DOSIMETRY, AND HEALTH RISKS

13.1 INTRODUCTION

This chapter integrates key information on exposure-dose-response risk assessment components drawn from the preceding detailed chapters, in order to provide a coherent framework for assessment of human health risks posed by ambient particulate matter (PM) in the United States. More specifically, this chapter first provides background information on key features of atmospheric particles, highlighting important distinctions between fine and coarse mode particles with regard to their size, chemical composition, sources, atmospheric behavior, and potential human exposure relationships—distinctions which collectively suggest that fine and coarse mode particles should be treated as two distinct subclasses of air pollutants. Information on recent trends in U.S. concentrations of different ambient PM size/composition fractions and ranges of variability seen in U.S. regions and urban air sheds is also summarized to place the ensuing health effects discussions in perspective.

The chapter next summarizes key points regarding respiratory tract dosimetry, followed by discussion of the extensive PM epidemiologic database that has evolved during the past several decades. The latter includes recent studies providing evidence that serious health effects (mortality, exacerbation of chronic disease, increased hospital admissions, etc.) are associated with exposures to ambient levels of PM found in contemporary U.S. urban air sheds even at concentrations below current U.S. PM standards. Evaluations of other possible explanations for the reported PM epidemiology results (e.g., effects of weather, other co-pollutants, choice of models, etc.) are also discussed, ultimately leading to the conclusion that the reported associations of PM exposure and effects are valid. Evidence is then reviewed that (a) clearly substantiates associations of such serious health effects with U.S. ambient PM_{10} levels and (b) less extensively points toward fine particles (as indexed by various indicators) as likely being important contributors to the observed human health effects. The overall coherence of the epidemiologic data base is also discussed, suggesting a likely causal role of ambient PM in contributing to the reported effects.

The nature of the observed effects and hypothesized potential mechanisms of action underlying such effects are then discussed in subsequent sections. The discussion of potential mechanisms of injury examines ways in which PM could induce health effects. The current limited availability of much experimental evidence necessary to evaluate or directly substantiate the viability of the hypothesized mechanisms is noted. Limited information concerning possible contributions of particular classes of specific ambient PM constituents is also summarized.

The chapter also provides information on the identification of population groups at special risk for ambient PM effects, factors placing them at increased risk, and other key components that need to be considered in generating risk estimates for the possible occurrence of PM-related health events in the United States. An examination of risk factors includes those affecting exposure risk and mechanistic determinants of dose, as well as individual factors affecting susceptibility related to age or disease.

One of the present problems of “integrating” PM health effects research results is the current disparity between evidence from epidemiologic studies and from experimental human exposure and laboratory animal studies. On the one hand, epidemiologists have examined relationships between regionally and temporally variable mixtures of ambient air particles and broad classes of health effects (e.g., mortality, hospital admissions, respiratory illness, etc.), whose target population largely includes the elderly and individuals with cardiopulmonary disease. Extremely high exposure levels associated with historic air pollution "disasters" indicate that severe illness and death are clearly linked with high levels of air pollution, including PM. Also, children have been studied for respiratory symptomatology and mechanical pulmonary function changes in relation to ambient PM concentrations. On the other hand, experimental human studies have focused mainly on reversible physiologic and biochemical effects in young healthy people that result from controlled exposures to laboratory-generated acidic aerosols, sulfates or nitrates. Laboratory animal studies cover a broader range of specific health endpoints than the human studies, but again typically evaluate individual particle species that comprise the ambient mixture called particulate matter and their effects on healthy animals. Much more experimental research data are needed on effects of ambient (or quasi-ambient) PM on diseased humans or animal models of disease.

13.2 AIRBORNE PARTICLES: DISTINCTIONS BETWEEN FINE AND COARSE PARTICLES AS SEPARATE POLLUTANT SUBCLASSES

As discussed in detail in Chapter 3 of this document, airborne PM is not a single pollutant but many classes of pollutants, each class consisting of several to many individual chemical species. One classification is based on the natural division of the atmospheric aerosol into fine-mode and coarse-mode particles. Fine-mode particles, in general, are smaller than coarse-mode particles, but they also differ in many other aspects such as formation mechanisms, chemical composition, sources, physical behavior, human exposure relationships, and control approaches required for risk reduction. Such differences alone are sufficient to justify consideration of fine-mode and coarse-mode particles as separate pollutants, regardless of the extent or lack of evidence regarding differences in composition, respiratory tract dosimetry, or associated health effects in laboratory animals or humans. Table 13-1 compares several key points that differentiate fine-mode and coarse-mode particles. Various physical and chemical differences between fine-mode particles and coarse-mode particles, their sources, factors affecting human exposure, and their respiratory tract deposition are also concisely summarized below as a prelude to more in-depth discussion of key health effects associated with ambient PM exposures and other information useful in assessing PM-related public health risks in the United States.

13.2.1 Size Distinctions

Three approaches are used to classify particles by size: (1) modes, based on formation mechanisms and the modal structure observed in the atmosphere; (2) size cut point, based on the 50% cut point of the specific sampling device; and (3) dosimetry, based on the ability of particles to enter certain regions of the respiratory tract. The modal structure is shown in Figure 13-1. In the ambient atmosphere the fine particle mode is composed of the nuclei mode and the accumulation mode. The nuclei mode is clearly observable only near sources of condensible gases. Particles in the nuclei mode rapidly grow into the accumulation mode but the accumulation mode does not grow further into the coarse particle mode. The lognormal distribution (in units of particle diameter) is frequently used to approximate the distribution of particle number, surface area, volume, or mass. The accumulation mode may contain varying amounts of ultrafine particles (≤ 0.1 μm) aggregated from the nuclei mode.

TABLE 13-1. COMPARISON OF AMBIENT FINE AND COARSE MODE PARTICLES

	Fine	Coarse
Formed from:	Gases	Large solids/droplets
Formed by:	Chemical reaction Nucleation Condensation Coagulation Evaporation of fog and cloud droplets in which gases have dissolved and reacted	Mechanical disruption (crushing, grinding, abrasion of surfaces, etc.) Evaporation of sprays Suspension of dusts
Composed of:	Sulfate, $SO_4^=$ Nitrate, NO_3^- Ammonium, NH_4^+ Hydrogen ion, H^+ Elemental carbon, Organic compounds (e.g., PAHs, PNAs) Metals, (e.g., Pb, Cd, V, Ni, Cu, Zn, Mn, Fe) Particle-bound water	Resuspended dusts (Soil dust, street dust) Coal and oil fly ash Oxides of crustal elements, (Si, Al, Ti, Fe) $CaCO_3$, NaCl, sea salt Pollen, mold, fungal spores Plant/animal fragments Tire wear debris
Solubility:	Largely soluble, hygroscopic and deliquescent	Largely insoluble and non-hygroscopic
Sources:	Combustion of coal, oil, gasoline, diesel, wood Atmospheric transformation products of NO_x, SO_2, and organic compounds including biogenic organic species, e.g., terpenes High temperature processes, smelters, steel mills, etc.	Resuspension of industrial dust and soil tracked onto roads and streets Suspension from disturbed soil, e.g., farming, mining, unpaved roads Biological sources Construction and demolition, coal and oil combustion, ocean spray
Atmospheric half-life:	Days to weeks	Minutes to hours
Travel distance:	100s to 1000s of km	<1 to 10s of km

Source: Adapted from Wilson and Suh (1996).

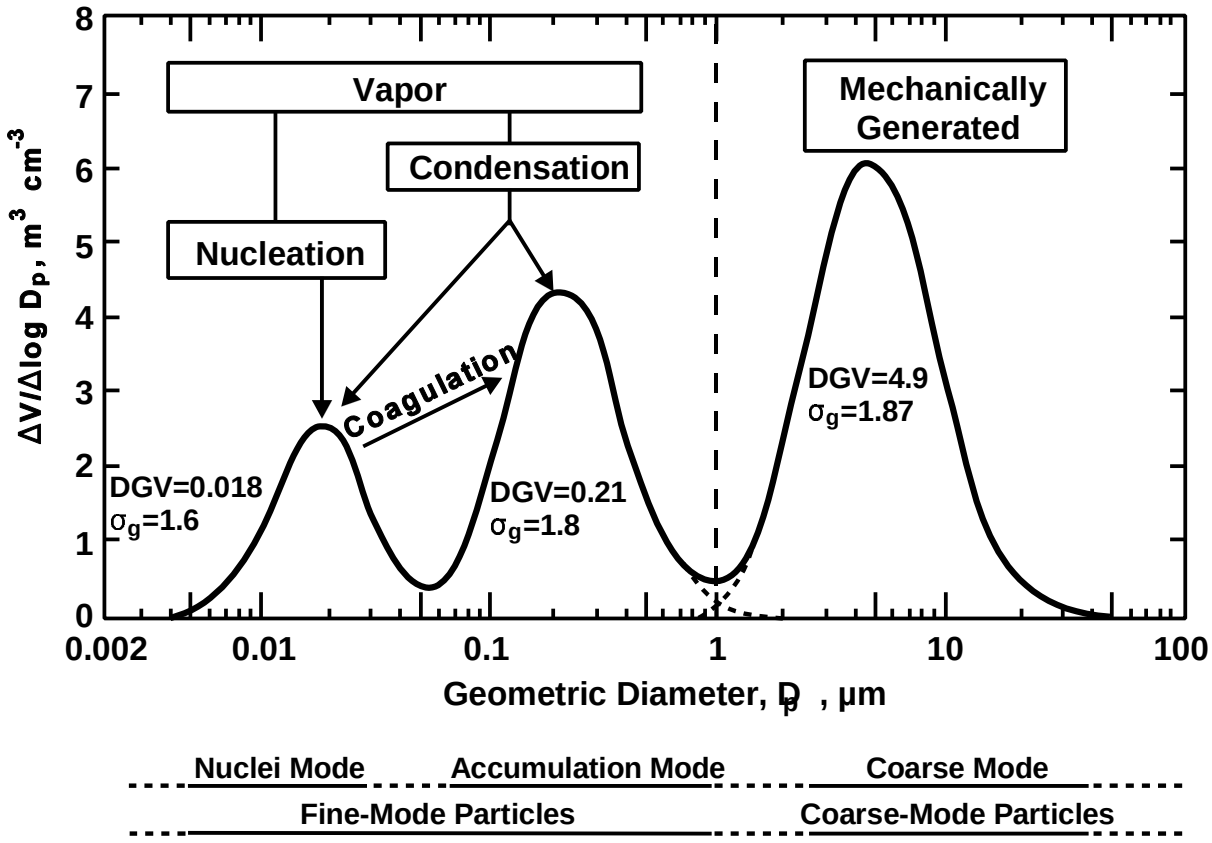

Figure 13-1. Measured volume size distribution showing fine-mode and coarse-mode particles and the nuclei and accumulation modes within the fine-particle mode. DGV (geometric mean diameter by volume, equivalent to volume median diameter) and σ_g (geometric standard deviation) are shown for each mode. Also shown are transformation and growth mechanisms (e.g., nucleation, condensation, and coagulation).

Source: Wilson et al. (1977).

Particle diameters are usually given as aerodynamic equivalent diameter, d_{ae}, defined as the diameter of a particle with equal settling velocity to that of a sphere with unit density (1 g/cm^3). This is the most appropriate diameter for discussion of lung deposition and particle collection. The accumulation mode typically has a mass median aerodynamic diameter (MMAD) of 0.3 to 0.7μm and a geometric standard deviation, σ_g (a measure of the size dispersion), of 1.5 to 1.8. The coarse particle mode may also contain multiple modes but they are not readily distinguished. Therefore, the coarse particle mode tends to have a broader size distribution, with a σ_g = 2.2 to 2.4. Measured MMADs typically range from 6 to 20 μm diameter in the ambient

atmosphere, but these values may be low because of the difficulty of collecting particles in the upper tail of the coarse-mode distribution.

The indicator for the current PM standard is PM_{10}. Since neither the respiratory tract nor particle samplers can separate particles with a sharp cut, PM_{10} is defined as having a 50% cutpoint at 10 μm d_{ae}. PM_{10} samplers collect all fine-mode particles. They collect a decreasing fraction of particles as the diameter increases above 10 μm d_{ae} and an increasing fraction of particles as the diameter decreases below 10 μm d_{ae}. The mass of the coarse fraction ranges from 20% of PM_{10} in some eastern urban areas to 80% of PM_{10} in dry western areas.

Agreement has been reached between the International Standards Organization (ISO) and American Council of Government Industrial Hygienists (ACGIH) who have also promulgated definitions of particle size fractions that are based on the ability of particles to penetrate to various depths within the respiratory tract (Vincent, 1995). Inhalable refers to particles which can enter beyond the external airway openings and, as discussed in Chapter 10, has a practical upper limit of 40 to 60 μm. Thoracic particles refer to those particles which can penetrate beyond the larynx; 50% of particles of 10 μm aerodynamic diameter will penetrate beyond the larynx.

The appropriate division between the fine and coarse fractions is not sharply defined, but falls in the range between 1.0 and 3.0 μm d_{ae}, where fine-mode and coarse-mode particles overlap but where particle mass is at a minimum. Thus, in general, particles less than 1.0 μm d_{ae} are fine-mode particles and particles greater than 2.5μm d_{ae} are coarse-mode particles. However, as the relative humidity approaches 100%, fine particles may grow beyond 1.0 μm and even beyond 2.5 μm d_{ae}; and, in very dry environments, it may also be possible to find particles less than 1.0 μm d_{ae} in the small size tail of the coarse particle mode. It is important to note that $PM_{2.5}$ may sometimes contain an appreciable quantity of coarse-mode particles in the 1 to 2.5 μm d_{ae} size range.

$PM_{2.5}$ particles are frequently referred to as fine, while the difference between $PM_{2.5}$ and PM_{10} ($PM_{10-2.5}$), is sometimes referred to as coarse or as the coarse fraction of PM_{10}. In the present discussion, fine-mode particles and coarse-mode particles are used to emphasize that important distinctions include not just size but also other additional fundamental differences in sources, formation mechanisms, and chemical composition.

13.2.2 Formation Mechanisms

Fine particles are formed from gases by nucleation (gas molecules coming together to form a new particle), by condensation (gas molecules condensing onto a pre-existing particle), or by liquid phase reactions. Gases may dissolve in a liquid droplet (either a solution particle or a cloud or fog droplet), react with another dissolved gas, and form a low vapor pressure product. When fog and cloud droplets evaporate, particulate matter remains, usually in the fine particle mode.

Coarse particles are formed by mechanical processes which produce small particles from large ones. Energy considerations normally limit coarse mode particle sizes to greater than about 1.0 μm d_{ae}.

Particles are designated as primary if they are emitted directly into the air as particles or as vapors which condense to form particles without chemical reaction. Examples of primary particles are (a) elemental carbon chain agglomerates formed during combustion and (b) chemical species such as lead, cadmium, selenium, or sulfuric acid which are volatile at combustion temperature but form PM rapidly as the combustion gases cool.

Particles are designated as secondary if they form following a chemical reaction in the atmosphere which converts a gaseous precursor to a product which either has a low enough saturation vapor pressure to form a particle or reacts further to form a low saturation vapor pressure product. Examples are the conversion of sulfur dioxide (SO_2) to sulfuric acid (H_2SO_4) which nucleates or condenses on existing particles, or the conversion of nitrogen dioxide (NO_2) to nitric acid (HNO_3) which may react further with ammonia (NH_3) to form particulate ammonium nitrate (NH_4NO_3).

Coarse particles are normally primary since they are formed by mechanical rather than by chemical processes. An exception is the reaction of acid gases with carbonate ($CO_3^=$) containing particles in which the $CO_3^=$ may be replaced by sulfate ($SO_4^=$), nitrate (NO_3^-), or chloride (Cl^-). Other exceptions are the reaction of HNO_3 with NaCl to form $NaNO_3$ and HCl gas and the reaction of SO_2 with wet NaCl to form Na_2SO_4 and HCl gas.

13.2.3 Chemical Composition

13.2.3.1 Fine-Mode Particulate Matter

In the ambient atmosphere, fine-mode particulate matter is mainly composed of varying proportions of six major components (sulfates, acids, nitrates, elemental carbon, organic carbon, and trace elements such as metals) and varying amounts of water.

Sulfates/Acid. Sulfur dioxide (SO_2), mainly from combustion of fossil fuel, is oxidized in the atmosphere to form sulfuric acid (H_2SO_4) particles. The H_2SO_4 may be partially or completely neutralized by reaction with ammonia (NH_3). Since the particles usually contain water, the actual species present are H^+, HSO_4^-, $SO_4^=$, and NH_4^+, in varying proportions depending on the amount of NH_3 available to neutralize the H_2SO_4. Particle strong acidity is due to free H^+ or H^+ available from HSO_4^- or H_2SO_4.

Nitrates. Nitrogen oxides (NO_x= NO + NO_2) are formed during combustion or any high temperature process involving air. The NO is converted to NO_2 by ozone (O_3) or other atmospheric oxidants. During the daytime, NO_2 reacts with the hydroxyl radical (OH) to form nitric acid (HNO_3). During nighttime, it forms nitric acid through a sequence of reactions involving ozone and the nitrate radical (NO_3). Ammonia reacts preferentially with sulfuric acid, but, if sufficient NH_3 is available, particulate ammonium nitrate (NH_4NO_3) will form.

Elemental Carbon. Chain agglomerates of very small elemental carbon (EC) particles are formed during combustion, such as in open hearth fireplaces, wood stoves and diesel engines.

Organic Carbon. Several heterogenous categories of organic carbon (OC) compounds are also often found in ambient air, as follows:

- **Primary-anthropogenic.** Incomplete combustion also leads to hundreds of organic compounds with low enough vapor pressure to be present in the atmosphere as particles, including mutagenic species such as polyaromatic hydrocarbons (PAHs).
- **Secondary-anthropogenic.** Some organic compounds, including aromatics (larger than benzene), cyclic olefins and diolefins, and other C_7 or higher hydrocarbons, react with O_3 or OH to form polar, oxygenated compounds with vapor pressures low enough to form particles.

- **Primary biogenic.** Viruses, some bacteria, and plant and/or animal cell fragments may be found in the fine mode.
    - **Secondary biogenic.** Terpenes, C_{10} cyclic olefins released by plants, also react in the atmosphere to yield organic particulate matter.

Trace Elements. A variety of transition metals and non-metals are volatilized during the combustion of fossil fuels, smelting of ores, and incineration of wastes and are emitted as fine particles (or vapors which rapidly form fine particles).

Water. Sulfates, nitrates, and some organic compounds are hygroscopic, i.e., they absorb water and form solution droplets. A variety of atmospheric pollutant gases can dissolve in the water component of the particle. This provides a mechanism for carrying into the lung species such as SO_2, H_2O_2, HCHO, etc., which, when in the gas phase, would normally be removed in the nose, throat, or upper airways.

13.2.3.2 Coarse-Mode Particulate Matter

Coarse-mode PM sources are primarily crustal, biological, or industrial in nature.

Crustal. Crustal material, from soil or rock, primarily consists of compounds that contain Si, Al, Fe, Mg, and K (small amounts of Fe and K are also found among fine-mode particles but come from different sources). In urban areas, much crustal material arises from soil which is tracked onto roads during wet periods and is suspended in the air by vehicular traffic. In rural areas, tilling, wind blowing over disturbed soil, or vehicles traveling on unpaved roads can generate coarse particles. Where farms have been treated with persistent pesticides or herbicides, these materials may also be present in suspended soil particles.

Biological. Biological materials such as bacteria, pollen, spores, and other plant and animal fragments are mostly found in the coarse size range (i.e., 2.0 to 10 μm d_{ae} for most, >20 μm d_{ae} for some).

Industrial. A variety of industrial operations generate coarse particles. Examples are construction and demolition, open pit mining, grain handling, coal handling, etc. Also, coal and oil combustion generate fly ash which is similar in chemical composition to soil and crustal material but can be differentiated by microscopic examination.

13.2.4 Atmospheric Behavior

Coarse-mode particles are large enough so that the force of gravity exceeds the buoyancy forces of the air. Therefore, large particles tend to rapidly fall out of the air. Coarse-mode particles are also too large to follow air streams, so they tend to be easily removed by impaction on surfaces. The atmospheric half-life of coarse particles depends on their size, but is usually only minutes to hours. However, vigorous mixing and convection, such as occurs during dust storms, can lead to longer lifetimes for the smaller size range of coarse-mode particles.

In contrast, fine-mode particles are small enough that gravitational forces are largely overcome by the random forces from collisions with gas molecules. Thus fine particles tend to follow air streams and are typically not removed by impaction. Accumulation-mode particles are sufficiently larger than gas molecules that their diffusion velocity is low. Removal by dry deposition is inefficient since they do not readily diffuse through the boundary layer of still air next to surfaces. Therefore, accumulation-mode particles have very long half-lives in the atmosphere, travel long distances, and tend to be more uniformly distributed over large geographic areas than coarse-mode particles. The atmospheric half-life of accumulation-mode particles with respect to dry deposition is on the order of weeks. Removal of accumulation-mode particles occurs when the particles absorb water, grow into cloud droplets, grow further to rain drops, and fall out as rain. This process reduces the atmospheric half-life of accumulation-mode particles to a few days.

Ultrafine or nuclei-mode particles, formed by nucleation of low saturation-vapor-pressure substances, tend to exist as disaggregated individual particles for very short periods of time (<minutes) in the ambient atmosphere due to rapid aggregation into accumulation- mode particles. Thus, ultrafine or nuclei-mode particles, possibly present in continuously supplied high concentrations near high temperature sources, tend to age rapidly into larger accumulation-mode particles that may be dispersed more widely over long distances.

13.2.5 Sources

The nature of fine and coarse PM sources are very different. Fine particulate matter is produced mainly by the condensation of gases in the high temperature environment of combustion chambers; the condensation of atmospheric precursor gases, some of which may undergo further reactions in particles; and the condensation of low vapor pressure photochemical

reaction products. Coarse particles, on the other hand, are produced mainly by the abrasion of surfaces (e.g., wind erosion, tire friction).

For a variety of reasons, concentrations of aerosol constituents measured at specific monitoring sites do not reflect the composition that would be obtained from a straightforward comparison of the source strengths shown in Chapter 5. Although windblown dust, from whatever source, represents the largest single category of PM_{10} emissions by mass (accounting for roughly 88% of the total), it does not often account for more than half of the mass of ambient samples. This discrepancy reflects in part the shorter residence time of dust in the atmosphere. Dust is found mainly in the coarse fraction, while secondary constituents are mainly found in the fine fraction. Monitoring sites are frequently located near specific sources such as roadways and less frequently away from areas where there is a perceived need for monitoring.

In general, emissions of primary PM_{10} components and gaseous precursors to PM_{10} are estimated to have decreased from 1984 to 1993. Ambient PM_{10} levels have also decreased in major urban areas during the same time period. However, a number of factors preclude a detailed comparison between trends in PM_{10} emissions and trends in ambient PM_{10} levels. These factors include long term variations in transformation rates of precursor gases to secondary particulate matter, wet and dry deposition rates, and effects of meteorological variability on dust emissions. As an example, nationwide emissions of dust by wind erosion decreased by almost a factor of eight between 1992 and 1993, because of the severe wet weather in the central United States. The large effect of meteorological variability on the magnitude of fugitive dust places severe constraints on the magnitude of trends in ambient dust concentrations that can be discerned. Because of the large secondary component of PM_{10} in the eastern United States, the concentration of PM_{10} reflects the emission of gaseous precursors by widely dispersed sources, followed by their conversion to particulate matter. The conversion of gases to secondary particulate matter occurs over distances of up to a few thousand kilometers, thereby uncoupling variability in the emissions of local sources from that of ambient concentrations.

13.2.6 Patterns and Trends in United States Particulate Matter Concentrations

PM_{10} Trends and Concentrations

Annual average PM_{10} mass concentrations throughout the United States, for different regions within the United States, and for most subregions or cities have generally decreased from 1988 to 1994. For the contiguous United States, the PM_{10} decrease has been greater in the western United States (approximately 30%) than in the eastern United States (about 15 to 20%). With few exceptions, the same range of percentage decreases have occurred for most subregions within the eastern and western United States. Smaller decreases in PM_{10} concentrations occurred for a few eastern subregions or cities and larger decreases in PM_{10} occurred for a few cities in the west. These decreases in annual average PM_{10} levels ranged from 25 to 35 $\mu g/m^3$ for all U.S. regions and most U.S. cities by 1994.

In general, annual mean PM_{10} concentrations in urban areas, found in EPA's Air Information Retrieval System (AIRS, 1995) database, are greater than about 20 $\mu g/m^3$. The highest annual mean concentrations in the eastern United States were found in Atlanta, GA; Paterson, NJ; Roanoke, VA; Philadelphia, PA; and Atlantic City, NJ. The overall annual mean concentration from these urban areas was about 34 $\mu g/m^3$. The five urban areas in the central United States with the highest annual mean concentrations were St. Joseph, MO; Steubenville, OH; Cleveland, OH; Omaha, NE; and Chattanooga, TN. The overall annual mean PM_{10} concentration for these five cities was 36 $\mu g/m^3$. The five areas with the highest annual mean PM_{10} concentrations in the western United States were Bakersfield, CA; Visalia, CA; Fresno, CA; Riverside, CA; and Stockton, CA. The average concentration in these five areas was about 50 $\mu g/m^3$. This value is significantly higher than corresponding values in the eastern and central United States. All averages given above were taken over the five year period from 1990 to 1994. At least one monitoring site was located in each area listed above, most areas had data from several sites. The sites themselves are located in areas representing a variety of different activities (e.g., industrial, commercial, agricultural and residential). The lowest annual mean PM_{10} concentrations found at sites in populated areas in the United States (Penobscot Co., ME; Marquette, MI; and Lakeport, CA) averaged about 12 $\mu g/m^3$ during the period from 1990 to 1994. Concentrations in all other areas in the United States fell within the limits given above.

All of the annual means stated above were calculated on the basis of sampling schedules that varied from every day to every sixth day, depending on the likelihood of exceedances of the PM_{10} NAAQS. The range of annual mean values shown above is consistent with the range found at the central sites used in the Harvard Six-City Study, where measurements were made every other day. The six cities along with their annual means are: Steubenville, OH (46.5 $\mu g/m^3$); Harriman, TN (32.5 $\mu g/m^3$); St. Louis, MO (31.4 $\mu g/m^3$); Topeka, KS (26.4 $\mu g/m^3$); Watertown, MA (24.2 $\mu g/m^3$); and Portage, WI (18.2 $\mu g/m^3$).

The lowest annual mean PM_{10} concentrations listed in AIRS (1995) were all below 10 $\mu g/m^3$. Examples of areas where annual mean concentrations this low were found include: Campbell Co., WY; Pima Co., AZ; Rosebud Co., MT; and Washington Co., ME. There was interannual variability in concentrations in these areas which sometimes resulted in annual averages greater than 10 $\mu g/m^3$ during the period from 1990 to 1994. At rural sites in national parks, wilderness areas, and national monuments, the annual average PM_{10} concentrations in the western United States during 1988 to 1991 were in the range of 5 $\mu g/m^3$ to 10 $\mu g/m^3$. Higher PM_{10} concentrations have been reported at some rural sites in the eastern United States. The corresponding $PM_{2.5}$ concentrations in western rural or remote sites were approximately 3 $\mu g/m^3$ and in eastern rural or remote sites were in the range of 5 $\mu g/m^3$ to 10 $\mu g/m^3$.

A few attempts to infer various types of "background" levels of $PM_{2.5}$ and PM_{10} have been made. The background levels most relevant to the present criteria document include a "natural background" which excludes all anthropogenic sources anywhere in the world, and a "background" which excludes anthropogenic sources in North America, but not elsewhere. Annual average natural background levels of PM_{10} have been estimated to range from 4 to 8 $\mu g/m^3$ in the western United States and 5 to 11 $\mu g/m^3$ in the eastern United States. Corresponding $PM_{2.5}$ levels have been estimated to range from 1 to 4 $\mu g/m^3$ in the western United States and from 2 to 5 $\mu g/m^3$ in the eastern United States. Twenty-four hour average concentrations may be substantially higher than the annual or seasonal average background concentrations presented in Chapter 6.

Fine and Coarse Particulate Matter Trends and Patterns

There are a few sites where information on both fine and coarse PM is available over extended time periods. Most of these data were obtained with dichotomous samplers which measure $PM_{2.5}$ and $PM_{10-2.5}$ (i.e., the coarse fraction of PM_{10}). Note that $PM_{2.5}$ will contain some coarse-mode particles as indicated earlier.

Examples were provided in Chapter 6 (Section 10) of $PM_{2.5}$ (fine), the coarse fraction of PM_{10} (coarse), and PM_{10} yearly arithmetic means and 90^{th} percentiles and, where daily data were available, daily or every 6^{th} day values for one year. Sources used are EPA's Aerometric Information Retrieval System, California Air Resources Board data, the Harvard Six-City data base, and the Harvard Philadelphia data base.

The Harvard Six-City Study provided data during 1980 to 1986. In the dirtier cities, Steubenville, St. Louis, and Harrison, there were decreases in all PM indicators, especially in the earlier years. There was also an apparent decrease in Topeka, one of the cleaner cities. No trend could be discerned in Watertown or Portage. It was difficult to determine whether there was a greater trend in fine or coarse particles.

AIRS provided some data on fine and coarse PM from 1989 to 1994. No significant trends were evident in $PM_{2.5}$ or $PM_{10-2.5}$ either in the means or the 90th percentile values. PM_{10} and $PM_{10-2.5}$ at the dirtier site in New York City appeared to have decreased from 1988 to 1992 but to have increased between 1992 and 1994. Other data from a number of sites in California from 1989 to 1995 also showed very slight downward trends for both fine and coarse PM. The California sites, however, showed substantial seasonal variability in both fine and coarse-mode particle concentrations.

Several data sets from Philadelphia were combined to show TSP trends from 1973 to 1990 and changes in fine and coarse PM from the 1980 period to the 1990 period. TSP came down rapidly between 1973 and 1981 and leveled off thereafter. Fine particle concentrations were approximately 30% higher in the 1980-1982 period than in the 1992-1993 period.

The data base of fine and coarse PM allowed an analysis of the fractions of PM_{10} due to both fine and coarse PM. The annual ratios of $PM_{2.5}$ to PM_{10} were within the range of 0.5 to 0.6 for most eastern U.S. urban stations, but there was considerable spatial and seasonal variability. In Philadelphia, the fine fraction of PM was fairly stable over the year.

During the 1993-1994 period, the mean $PM_{2.5}/PM_{10}$ ratio was 0.71, with a coefficient of variation (CV) of 18%. In contrast, the fine fraction of PM_{10} was seasonally quite variable in California, in general being higher in the winter and lower in the summer. For example, a mean ratio of 0.50 and CV of 26% was found in Azusa, a mean ratio of 0.44 and CV of 43% in Bakersfield, and a mean of 0.29 and CV of 34% for El Centro. This illustrates limitations in trying to infer $PM_{2.5}$ concentrations from PM_{10} or TSP measurements unless site-specific ratios are available. The ratio of $PM_{2.5}$ to PM_{10} values may vary substantially from location to location or from one season to another at the same site.

Day-to-Day Variability of PM Concentrations

The only data set from which the daily variability in $PM_{2.5}$ and PM_{10} concentrations could be assessed, based on daily measurements, was obtained in Philadelphia, PA from 1992 to 1995. Average day-to-day concentration differences obtained were 6.8±6.5 $\mu g/m^3$ for $PM_{2.5}$ and 8.6±7.5 $\mu g/m^3$ for PM_{10}. Maximum day-to-day differences obtained were 54.7 $\mu g/m^3$ for $PM_{2.5}$ and 50.4 $\mu g/m^3$ for PM_{10}.

13.2.7 Community and Personal Exposure Relationships

As discussed in Chapters 6 and 7, atmospheric behavior differences between fine-mode and coarse-mode particles lead to important differences in relationships between personal exposure and ambient concentrations measured at a central fixed-site monitor. Fine particles tend to have long atmospheric half-lives, can travel long distances, and therefore can result from distant or widely distributed sources. Evidence from one eastern city, Philadelphia, suggests that the concentrations of fine particles may be uniform over that urban area. Therefore, a measurement at one site may give a reasonable estimate of the fine particle concentration across a city or even wider regional areas, assuming the site is not unduly influenced by a local source of fine particles. Coarse particles, however, have more localized and variable sources and because such particles are rapidly removed, their concentration decreases with distance from the source and the distribution may not be uniform across a city or region. Thus, people in one part of a city may experience high concentrations of coarse fraction particles on one day while people in a different part of the city may experience high concentrations on another day, even though the city-wide average

concentration may be the same on both days. This unevenness of coarse mode particles across a city may need to be taken into account when assessing health impacts in community epidemiological studies.

A further consideration arises with regard to relationships between ambient (outdoor) PM concentrations and personal or indoor exposures. Because people spend most of their time indoors, the particle concentrations indoors tend to dominate personal exposures. However, indoor exposure is due both to particles generated indoors and to ambient particles generated outdoors but which have infiltrated indoors. Major indoor sources of fine particles are smoking and cooking. The major indoor sources of coarse particles are indoor activities that resuspend previously settled PM and that stir up and suspend other materials, including a variety of biological materials such as mold spores and insect debris. Household cleaning, especially dusting and vacuuming, can dramatically increase coarse particle concentrations. When doors and windows are open, both fine-mode and coarse-mode particles will penetrate from outdoors to indoors. When doors and windows are closed, particle penetration might be expected to be dependent on size and air exchange rate, but two experimental studies (Thatcher and Layton, 1995; Koutrakis et al., 1993) suggest that particle penetration may be independent of particle size up to about 10 μm d_{ae}. Once indoors, however, particle size becomes important. Coarse-mode particles are rapidly removed by deposition, whereas accumulation-mode particles have longer half-lives. The production of indoor-generated particles is controlled by daily indoor activities. Therefore, the exposure to indoor-generated particles will not be correlated with the concentration of ambient (outdoor-generated) particles, and time-series epidemiology based on ambient measurements are unlikely to identify health effects related to indoor-generated particles.

The various penetration and removal processes can be modeled, and the equilibrium ratio of the concentration of ambient particles which have penetrated indoors and remained suspended to the concentration of ambient particles outdoors (called the infiltration ratio) can be calculated as a function of the air exchange rate, the penetration factor (assumed to be 1.0 for PM < 10 μm), and the removal rates which are a function of particle size. Infiltration ratio calculations, based on data from the Particle Total Exposure Assessment Methodology Study (PTEAM), reviewed in Chapter 7, are graphically depicted in Figure 13-2. As is evident, the infiltration ratio of sulfate, which is almost completely of outdoor origin and

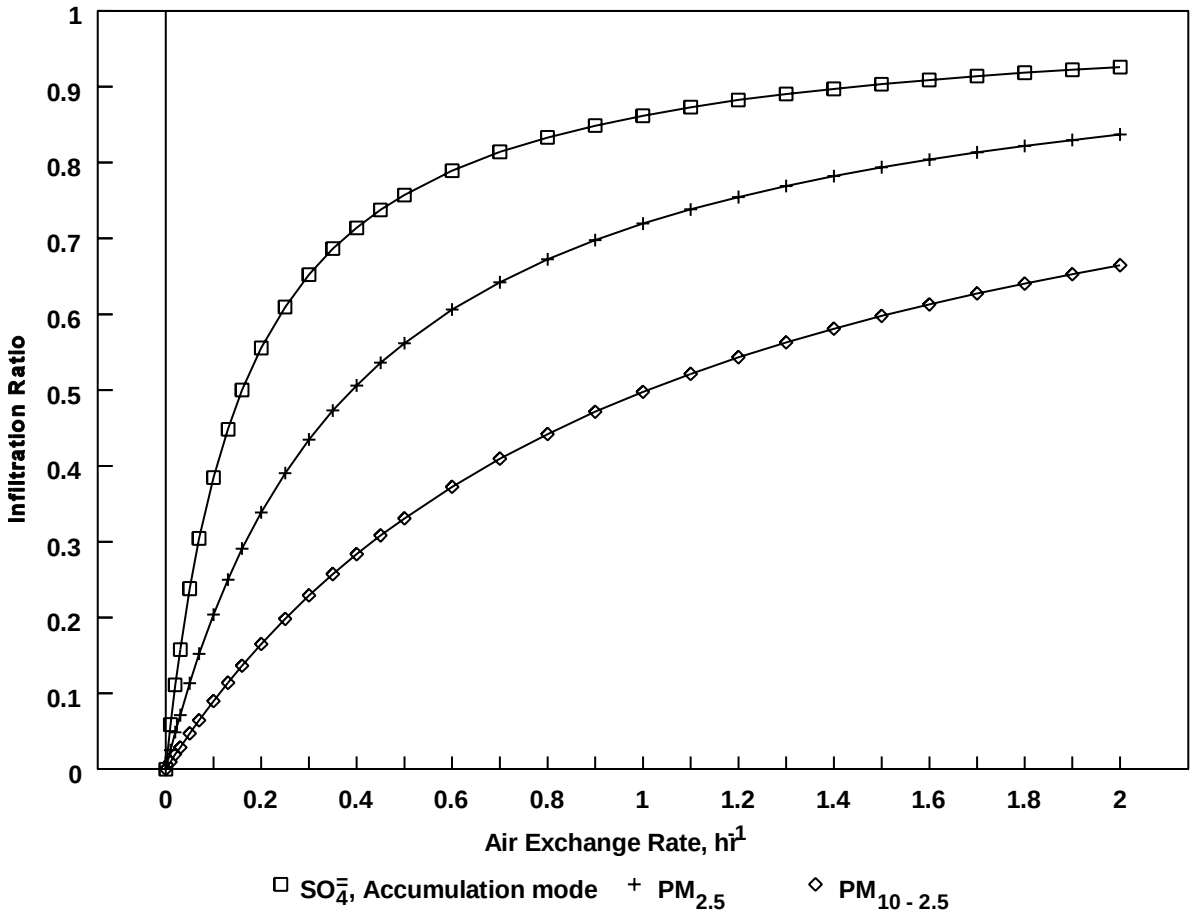

Figure 13-2. Ratio of indoor concentration of ambient PM to outdoor concentration (infiltration ratio) for sulfate (an indicator of accumulation-mode particles), $PM_{2.5}$, and the coarse fraction of PM_{10} ($PM_{10-2.5}$), as a function of air exchange rate. Based on data from PTEAM.

expected to be in the fine-mode, is greater than that of $PM_{2.5}$, which may contain some coarse-mode material from both indoor and outdoor sources and thus have a larger effective d_{ae} than sulfate. $PM_{2.5}$ in turn has a greater infiltration ratio than $PM_{10-2.5}$.

The more uniform distribution of ambient fine-mode particles across a city and the higher infiltration ratio for fine particles, means that an ambient measure of fine particles at a central site may provide a useful estimate of the average exposure of people in the community to ambient fine-mode particles. For example, experimental data on personal exposure to sulfate, which are predominantly of outdoor origin and in the fine-mode particle size range, show consistently high correlation of total human exposure to sulfate with outdoor central-site

measurements of ambient sulfates ($0.78 < R^2 < 0.92$) (Suh et al., 1993). However, because of the non-uniform regional concentrations and lower infiltration ratios, an ambient measure of coarse particles at a central site may not provide nearly as good an indication of exposure of people in the community to ambient coarse particles. Much of the time-series epidemiology currently available is based on ambient TSP or PM_{10} measurements, which represent the sum of fine and coarse (in the case of TSP) or the sum of fine particles and the coarse-mode fraction of PM_{10} (in the case of PM_{10}). In Philadelphia, and to a lesser extent some other cities (where PM_{10} is not dominated by coarse wind-blown dust), it has been shown that TSP and PM_{10} concentrations correlate better with $PM_{2.5}$ concentrations than with the coarse fraction of PM_{10}. It is thus possible that the observed statistical relationships between various ambient particle indicators and health outcomes are largely due to an underlying relationship between fine-mode particles and health outcomes. This hypothesis is supported by recent epidemiological analyses for cities where both $PM_{2.5}$ and $PM_{10-2.5}$ data are available (Schwartz et al., 1996a).

13.3 CONSIDERATION OF FACTORS AFFECTING DOSIMETRY

Because the tissue dose of a putative toxic moiety is not always proportional to the ambient exposure of a compound and because the response is more likely related to the tissue dose, contemporary health risk assessment emphasizes the need to clearly distinguish between exposure concentration and internal doses to critical target tissues. The term "exposure-dose-response" assessment has been recommended as more accurate and comprehensive (Andersen et al., 1992). Characterization of the exposure-dose-response continuum is advocated as a way to reduce the uncertainty in extrapolations required from laboratory animal data or from typical humans to susceptible members of the human population. In the case of PM, such characterization requires the elucidation and understanding of the mechanistic determinants of particle deposition and clearance, toxicant-target interactions, and tissue responses.

13.3.1 Factors Determining Deposition and Clearance

Particles are deposited in the respiratory tract by mechanisms of impaction, sedimentation, interception, diffusion, and electrostatic precipitation. Differences in ventilation rates, in the upper respiratory tract structure, and in the size and branching pattern of the lower respiratory

tract between species and among humans of different ages and disease states result in significantly different patterns of particle deposition due to the effects of these geometric variations on air flow patterns. The relative contribution of each deposition mechanism to the fraction of particles deposited varies for each region of the respiratory tract (extrathoracic, ET; tracheobronchial, TB; and alveolar, A). Air flow in the ET region is characterized by high velocity and abrupt directional changes, so that the predominant deposition mechanism in this region is inertial impaction. Although, for ultrafine particles, the dominant mechanism in the ET region is diffusion. In the A region, diffusional deposition is also important since many smaller particles penetrate to this region.

Disposition and retention of initially deposited particles depends on clearance and translocation mechanisms that also vary with each region of the respiratory tract. Sneezing and nose wiping or blowing and mucociliary transport to the gastrointestinal tract via the pharynx are important clearance processes for particles deposited in the ET region, whereas coughing, mucociliary transport, endocytosis by macrophages or epithelial cells and dissolution and absorption into the blood or lymph are important in the TB region. Smoking reduces the rate of respiratory tract clearance. Endocytosis by macrophages or epithelial cells and dissolution and absorption into the blood or lymph are the dominant mechanisms in the alveolar region. Depending on their solubility, particles deposited in the alveolar region could have long residence times. The ultimate disposition and retention of a deposited dose is thus dependent on the initial site of deposition, physicochemical properties of the particles (e.g., solubility), and on time since deposition.

The influence of different airway geometry on airflow patterns and subsequent deposition have been documented both empirically and with theoretical modeling. Simulations discussed in Chapter 10 suggest deposition differences among children and adults, with adolescents (age 14 to 18) predicted to have greater respiratory tract daily mass deposition (μg/d) of submicron particles than adults. Changes in respiratory tract architecture, especially in the smaller conducting airways and gas exchange regions, can be critical factors affecting the dosimetry of inhaled particles. Ambient particles will be deposited in the lung to varying degrees depending on their aerodynamic and physicochemical properties. Changes in architecture or geometry of the respiratory tract

with disease affect airflow and thereby the aerodynamic behavior of inhaled particles. A mismatch of ventilation and perfusion in lung diseases, such as emphysema, chronic obstructive pulmonary disease (COPD), and asthma has been noted (Bates et al., 1971; Bates, 1989). Chronic bronchitis, emphysema, and chronic airways obstruction all fall within the aegis of COPD, and both it and asthma result in altered airflow. In more severe stages of these diseases, the healthy portion of the lung receives more of the tidal volume which can result in some ventilatory units receiving an increased particle burden compared to others. Kim et al. (1988) demonstrated greater particle deposition, using an aerosol rebreathing test, in COPD patients versus healthy subjects. The increase in deposition correlated with the degree of airway obstruction. Anderson et al. (1990) also showed that the deposition of ultrafine particles in patients with COPD is greater than in healthy subjects. Svartengren et al. (1994) showed enhanced deposition in asthmatics. Bennett et al. (1996) reported a greater deposition rate (particles/time) in COPD patients relative to healthy subjects and that these patients under resting breathing conditions receive an increasing dose of inhaled fine particles with increased severity of their airways disease. Model simulations discussed in Chapter 10 predict that dose expressed in terms of numbers of particles per anatomical unit would be increased in individuals with compromised lungs relative to healthy subjects (Miller et al., 1995).

Not only may patients with preexisting COPD be susceptible because of an enhanced or altered deposited dose pattern, but their disease may also predispose these patients to altered responses to the toxic effects of ambient PM (discussed in the next section). To the extent that cigarette smoke contributes to changes in architecture and response, smokers can also be considered a potentially susceptible population for the effects of PM.

Physicochemical characteristics of particles (e.g., particle diameter, distribution, hygroscopicity) interact with the anatomic (e.g., branching pattern) and physiologic (e.g., ventilation rate, clearance processes) factors to influence deposition and retention of inhaled aerosols. For a given aerosol, the two most important parameters which characterize size distribution, and hence deposition, are the MMAD and the σ_g of the particles. It must be emphasized that the relative contribution of these anatomic, physiologic, and physicochemical determinants is a dynamic relationship. Further, the relative contribution of these determinants is also influenced by exposure conditions such as concentration and duration.

The influence of the particle size distribution on the fraction of particles deposited in the respiratory tract is illustrated in Figure 13-3. This figure depicts the predicted deposition fractions for an adult male, using a general population ventilation activity pattern, in the alveolar (A), tracheobronchial (TB), and thoracic (A + TB) regions. The difference between total respiratory tract and total thoracic deposition fractions represents the extrathoracic (ET) or upper airway deposition fraction. The deposition fraction in the respiratory tract, relative to unit mass concentration in air, is shown for particles of different MMAD, in the range of 0.1 to 100 μm, for two different geometric standard deviations (σ_g = 1.8 in the top panel and σ_g = 2.4 in the bottom panel).

These simulations show that alveolar deposition fraction is fairly uniform for aerosols between 0.5 and 4.0 μm MMAD. Deposition fraction of particles in the A region increases for particles less than 0.5 μm because diffusion becomes the dominant mechanism. In the aerodynamic range of particles ($\geq$ 1.0 μm MMAD), deposition fraction increases as particle size increases and sedimentation and impaction become important deposition mechanisms, especially for the larger particles (> 5 μm MMAD) in the TB region. This pattern is altered slightly for mouth breathing versus normal breathing, in that mouth breathers have a greater TB deposition of particles greater than 2.5 μm (i.e., the coarse fraction of PM_{10}) than they would if breathing PM only via the nose. The pattern is also influenced by the degree of dispersion of the particle sizes. Polydispersity decreases the deposition fraction of particles in the aerodynamic range as shown by decrements in the bottom panel for the polydisperse aerosol (σ_g = 2.4) compared to the more monodisperse aerosol (σ_g = 1.8) in the top panel.

The collection fraction for PM_{10} and $PM_{2.5}$ samplers are also depicted in Figure 13-3. As considered for the basis of the previous PM standard, the PM_{10} sampler collection curve shows that this sample accounts well for thoracic (TB + A) deposition but excludes many of the larger particles which would be deposited in the ET region. Also, the $PM_{2.5}$ cutpoint does not capture some larger particles that would be deposited in the TB and A regions, especially in mouth breathers under the simulated conditions. These simulations corroborate that the 10 μm cut point is appropriate to separate ambient particles that have the potential to deposit in the lower respiratory tract versus those in ET regions. However, these results also

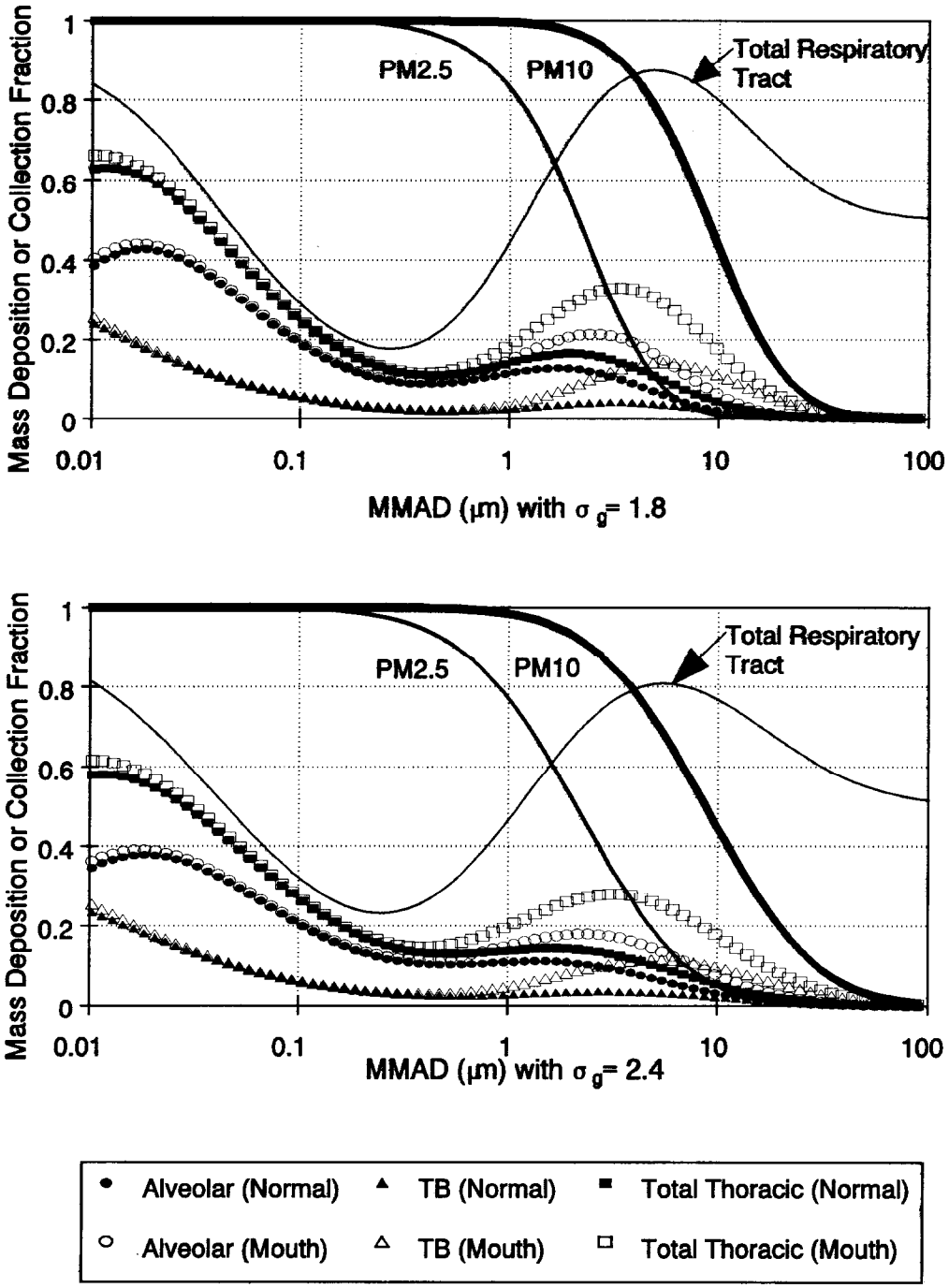

Figure 13-3. Human respiratory tract PM deposition fraction and PM_{10} or $PM_{2.5}$ sampler collection versus mass median aerodynamic diameter (MMAD) with two different geometric standard deviations (σ_g = 1.8 or σ_g = 2.4). Alveolar, tracheobronchial, or total thoracic deposition fractions predicted for normal augmenter versus mouth breather adult male using a general population (ICRP66) minute volume activity pattern and the 1994 ICRP66 model.

suggest that an intermediate cut point that is directly comparable to separation of fine- and coarse-mode particles is not supported on the basis of considering particle deposition alone, due to the fact that particles in the coarse fraction of PM_{10} also have some efficiency for deposition in both the A and TB regions. As discussed previously, construction of the exposure-dose-response continuum is also dependent on defining a dose metric that is relevant to the mechanism of action for a compound.

13.3.2 Factors Determining Toxicant-target Interactions and Response

Differences in susceptibility can be due to factors influencing deposited and retained particle mass or number, toxicant-target interaction, or tissue sensitivity (e.g., conditions causing altered or enhanced target tissue response). Discussion of various individual risk factors that might influence tissue response to a delivered dose is provided in Section 13.6. Since the target tissue has been identified as the lower respiratory tract, however, some generalizations for the definition of dose can be useful in trying to ascertain if one metric may be more appropriate than another to describe a given toxicant-target interaction.

The biologically-effective dose resulting from inhalation of particles can be defined as the time integral of total inhaled particle mass, particle number, or particle surface area per unit of respiratory tract surface area or per unit mass of the respiratory tract. Choice of the metric to characterize the biologically-effective dose should be motivated by insight into the mechanisms of action of the compound (or particles) in question. The biologically-effective dose may be accurately described by particle mass or number deposition alone if the particles exert their primary action on the surface contacted (Dahl et al., 1991). For longer-term effects, the deposited dose may not be a decisive metric, since particles clear at varying rates from the different respiratory tract regions. When considering the epidemiologic data, dose metrics could be separated into two major categories, pattern and quantity of acute deposition and the pattern and quantity of retained dose. The deposited dose may be more important for daily mortality, hospital admissions, work loss days, etc. On the other hand the retained dose may be more important for chronic responses such as induction of chronic disease, shortening of life-span ("premature" mortality), or diminished quality of life although repeated acute responses may also be related to chronic responses.

To date, most analyses have relied upon the particle mass concentration ($\mu g/m^3$) breathed by exposed individuals. If relative risk (RR) estimates were calculated based on various internal dose metrics (e.g., deposited dose [mass] normalized per unit tracheobronchial or alveolar surface area or normalized per critical cell type such as the alveolar macrophage), some of these relationships could change or be modified. Moreover, not only is there a question about how the doses should be normalized (e.g., by body mass, lung epithelial surface area, etc.), but also as to whether the PM dose should be expressed as numbers of particles, aggregate particle surface area, or total particle mass in a given size fraction. The fine fraction contains by far the largest number of particles, and those particles generally have a larger aggregate surface area than coarse-mode particles. Such considerations may be important when trying to ascertain the appropriate dose metric for evaluation of lower respiratory tract health outcomes. For example, retardation of alveolar macrophage phagocytosis due to particle overload appears to be better correlated with particle surface area than particle mass (Morrow, 1988; Oberdörster et al., 1995a,b). Also, ultrafine particles have been shown to be less effectively phagocytosed by macrophages than larger particles (Oberdörster et al., 1992a,b).

Figure 13-4 presents an example which illustrates the complexities of considering PM "dose" using different metrics (e.g., such as mass, surface area, and number of particles) that are typical for a Southern California urban aerosol (Whitby, 1978). For the accumulation mode, which constitutes about 40% of the total mass in the illustrated sample, the geometric mean for the volume distribution, DGV, equivalent to the volume median diameter, is 0.31 μm. When the median diameter is expressed in terms of surface area, or count, the respective median diameters of the fine mode are 0.19 μm and 0.07 μm. By far the largest number of particles are contained in the nuclei mode, which is inconsequential in terms of mass. It must be remembered that the composition of the particles in each mode is different as are their hygroscopicity, solubility, translocation pathways, and toxicity.

Table 13-2 shows the predicted deposition efficiency in various regions of the respiratory tract for the aerosol depicted in Figure 13-4, which illustrates different particle diameters and size distributions that are typical of the nuclei, accumulation, and coarse modes of ambient particles. These are predicted from simulations as performed in

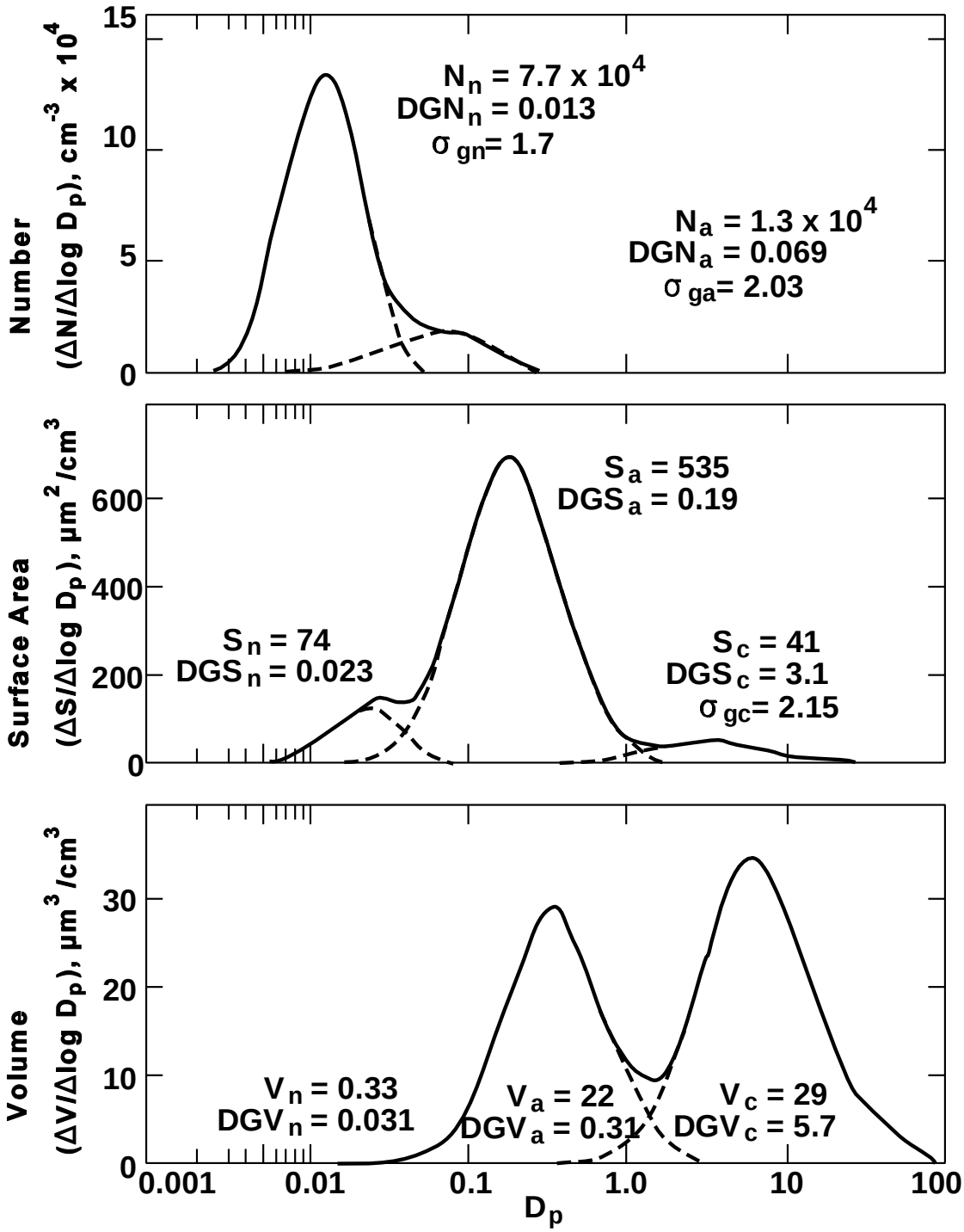

Figure 13-4. Distribution of coarse (c), accumulation (a), and nuclei or ultrafine (n), mode particles by three characteristics, volume (V), surface area (S), and number (N). DVG = geometric mean diameter by volume; DGS = geometric mean diameter by surface area; DGN = geometric mean diameter by number; D_p = geometric diameter.

Source: Whitby (1978).

TABLE 13-2. PREDICTED RESPIRATORY TRACT DEPOSITION AS A PERCENTAGE OF TOTAL INHALED MASS FOR THE THREE PARTICLE SIZE MODES IN THE AEROSOL DEPICTED IN FIGURE 13-4

	MMAD = 0.029 μm	MMAD = 0.27 μm	MMAD = 6.9 μm
	σ_g = 1.7	σ_g = 2.03	σ_g = 2.15
	ρ = 1.4 g cm^{-3}	ρ = 1.2 g cm^{-3}	ρ = 2.2 g cm^{-3}
Deposition Site	Nuclei Mode	Accumulation Mode	Coarse Mode
Extrathoracic Region	0.05	1.8	52.5
Tracheobronchial Region	0.07	0.8	2.1
Alveolar Region	0.02	2.8	3.4
Exhaled	0.02	23.8	12.4

[a]Dynamic shape factor (used to calculate MMAD from measured MMD) assumed for all three particle size modes to be 1.5 (ICRP, 1994).
MMD = mass median diameter (equivalent geometric).
MMAD = mass median aerodynamic diameter.
σ_g = geometric standard deviation.
ρ = particle density.

Chapter 10 for the aerosols of Phoenix, AZ and Philadelphia, PA. The patterns are different for the different modes.

How could particle size be important in biological activity? The mass of the particle may be important if the mechanism of action of the particle is related to its persistence. For example, large acid droplets require a much longer time to undergo neutralization than very small droplets and therefore would be more likely to reach intrathoracic airways as acid rather than as a neutralization product. Larger particles will take longer to dissolve or to be degraded enzymatically. If presentation of active groups to cell surfaces is important in the mechanisms of action, then the total surface area of the particles may be important. The largest aggregate surface area is contained in the accumulation mode. The particle mode with the largest surface area will be able to present the largest number of reactive surface groups to the cell surface. This feature would presumably be most important for relatively less soluble particles. Biological effects on epithelial cells or macrophages may depend on

the number of cell surface receptors that are stimulated or occupied. The number of particles may be related to their toxic effect. For example, if the number of separate phagocytotic events determines the capacity of a cell to ingest particles, then number becomes important. Numbers may also be important with regard to particles interacting with surface receptors of epithelial or phagocytic cells.

13.3.3 Construction of Exposure-Dose-Response Continuum for PM

It is clear that the characterization of the exposure-dose-response continuum from PM exposure data to human morbidity/mortality risk is far from complete. As defined by the National Research Council Board on Environmental Studies and Toxicology, a "biologic marker" is any cellular or molecular indicator of toxic exposure, of an adverse health effect, or of susceptibility (National Research Council, 1987). The markers represent signals — generally biochemical, molecular, genetic, immunologic, symptomatic (e.g., cough), or physiologic — in a continuum of events between a causal exposure and resultant disease.

The events in the progression from exposure to disease are not necessarily discrete, nor the only events in the continuum, and represent a conceptual temporal sequence. The paradigm of a continuum is only meant to illustrate a single pathway among many pathways to a biologic endpoint from a given exposure. Whether the progression is exactly linear or some other form, such as a multidimensional network, is debatable (Schulte, 1989). In most exposure-disease relationships, the linear causal sequence is an implied framework for research purposes. Appraisal of the validity of the components of the sequence requires that the framework be made explicit and that the existence of causal relationships be tested. That is, to better model the situation, one would consider that there may be multiple pathways leading to a given disease outcome. This is especially true for the etiology of most ambient air pollution-related biomedical outcomes. The effect of interest is often small in comparison to effects of other etiologic factors, and exposure itself may be confounded with that to other compounds and by inadequate characterization of temporal relationships.

Many advances in the understanding and quantification of the mechanistic determinants of toxicant-target interactions and tissue responses (including species sensitivity) are required before an overall model of a pathogenesis continuum can be constructed for ambient air PM. As our understanding is supplemented by identification of intervening relationships and components

are characterized more precisely or with greater detail, health events are less likely to be viewed as dichotomous (e.g., death or not; presence or absence of disease) but rather as a series of changes in a continuum from homeostatic adaptation, through dysfunction, to disease and death. The critical effect could become that biologic marker deemed most pathognomonic or of prognostic significance, based on a validated hypothesis of the role of the marker in the development of disease. As more causal component linkages are identified, it becomes more possible to elucidate quantitative relationships of the kinetics, natural history, and rates of transition along the continuum. Multiple markers may be more efficacious than a single marker for characterizing any given component.

Supplementary independent studies (typically toxicological), required to establish the validity of postulated intermediate components (markers) between exposure and disease, relevant to the observed mortality and morbidity in PM epidemiologic investigations, have been encumbered by methodologic difficulties. For example, differences in dosimetry due to altered flow patterns caused by geometric variation of the respiratory tract in different species have important implications for interspecies extrapolation. Toxicological data in laboratory animals typically can aid the interpretation of human clinical and epidemiological data because they provide concentration- and duration-response information on a more complex array of effects and exposures than can be evaluated in humans. However the use of laboratory animal toxicological data has typically been limited because of difficulties in quantitative extrapolation to humans. The various species used in inhalation toxicological studies do not receive identical doses in comparable respiratory tract regions (ET, TB, A) when exposed to the same aerosol (same composition, mass, concentration, and size characteristics). Such interspecies differences are important because the adverse toxic effect is likely related more to the quantitative pattern of deposition within the respiratory tract than to the exposure alone; this pattern determines not only the initial respiratory tract tissue dose, but also the specific pathways by which the inhaled particles are cleared and redistributed. Until these differences can be quantified, these dosimetric interspecies differences will impede characterization of the exposure-dose-response continuum for PM components and mixtures.

Another difficulty in elucidating the exposure-dose-response continuum using laboratory animal data is that different endpoints are typically assayed in the laboratory animals and the

relationship of these endpoints to the human health outcomes of interest have not been established. For example, the epidemiological studies evaluate endpoints such as illness, hospital admissions, and emergency room/doctor visits whereas the homologous biochemical or pathological endpoints in the laboratory animal models are unknown. Although the ultimate goal, for example, may be to estimate the responses of elderly persons with cardiopulmonary disease, most laboratory animal studies are normally performed on homogeneous populations of healthy animals and the majority of human clinical studies are performed on healthy young subjects or those with only mild disease.

In summary, until the mechanism(s) of action for effects induced by ambient PM or its important constituents can be characterized, the linkage between exposure and response provided by dosimetry will remain weak and only qualitative at best. Until dose metrics can be defined that correlate well with PM mechanism(s) of action, insights from dosimetry will be limited. Clearly, inhaled dose is important, but the best exposure/dose metric(s) to relate quantitatively to acute or chronic health outcomes awaits elucidation of pertinent mechanisms. Should the dose be normalized to regional surface area, for example, or expressed relative to some other critical mechanistic determinant (e.g., possibly per alveolar macrophage)? Once pertinent mechanism(s) of action are delineated, different biomedical indices can be used to characterize intermediate linkages to mortality or morbidity outcomes and to quantify relationships across the exposure-dose-response continuum. Towards that ultimate objective, both improved epidemiologic studies, using more refined measures of PM exposure (e.g., for fine versus coarse mode fractions of PM_{10}, for ultrafine particles, for particle number concentration, or for various classes of chemical constituents) and more laboratory animal studies evaluating effects of real-world concentrations of ambient PM mixtures or constituents are needed.

13.4 HEALTH EFFECTS OF PARTICULATE MATTER

This section evaluates available scientific evidence regarding the health and physiologic effects of exposure to ambient PM. The main objectives of this evaluation are as follows: (1) to summarize and evaluate the strengths and limitations of available epidemiologic findings; (2) to assess the biomedical coherence of findings across studied endpoints and

scientific disciplines; (3) to evaluate the plausibility of available evidence in light of mechanistic, pathophysiologic, and dosimetric considerations; and (4) to assess the extent to which observed effects can be attributed to PM and to specific size fractions and chemical constituents within the PM complex. Epidemiologic findings are emphasized first because they provide the largest body of evidence directly relating ambient PM concentrations to biomedical outcomes.

By far the strongest evidence for ambient PM exposure health risks is derived from epidemiologic studies. Many epidemiologic studies have shown statistically significant associations of ambient PM levels with a variety of human health endpoints, including mortality, hospital admissions and emergency room visits, respiratory illness and symptoms measured in community surveys, and physiologic changes in mechanical pulmonary function. Associations of both short-term and long-term PM exposure with most of these endpoints have been consistently observed. The general internal consistency of the epidemiologic data base and available findings have led to increasing public health concern, due to the severity of several studied endpoints and the frequent demonstration of associations of health and physiologic effects with ambient PM levels at or below the current U.S. NAAQS for PM_{10}. The weight of epidemiologic evidence suggests that ambient PM exposure has affected the public health of U.S. populations. However, there remains much uncertainty in the published data base regarding the shapes of PM exposure-response relationships, the magnitudes and variabilities of risk estimates for PM, the ability to attribute observed health effects to specific PM constituents, the time intervals over which PM health effects are manifested, the extent to which findings in one location can be generalized to other locations, and the nature and magnitude of the overall public health risk imposed by ambient PM exposure.

The etiology of most air pollution-related health outcomes is highly multifactorial, and the effect of ambient air pollution exposure on these outcomes is often small in comparison to that of other etiologic factors (e.g., smoking). Also, ambient PM exposure in the U.S. is usually accompanied by exposure to many other pollutants, and PM itself is composed of numerous physical and chemical components. Assessment of the health effects attributable to PM and its constituents within an already-subtle total air pollution effect is difficult even with well-designed studies. Indeed, statistical partitioning of separate pollutant effects may

somewhat artificially describe the etiology of effects which actually depend on simultaneous exposure to multiple air pollutants. Furthermore, identification of anatomic sites at which particles trigger end-effects and elucidation of biological mechanisms through which these effects may be expressed are still at an early stage. Thus, it remains difficult to form incisive a priori hypotheses to guide epidemiologic and experimental research. Lack of clear mechanistic understanding also increases the difficulty with which available findings can be integrated in assessing the coherence of PM-related evidence.

In this regard, several viewpoints currently exist on how best to interpret the epidemiology data: one sees PM exposure indicators as surrogate measures of complex ambient air pollution mixtures and reported PM-related effects represent those of the overall mixture; another holds that reported PM-related effects are attributable to PM components (per se) of the air pollution mixture and reflect independent PM effects; or PM can be viewed both as a surrogate indicator as well as a specific cause of health effects. In any case, reduction of PM exposure would lead to reductions in the frequency and severity of the PM-associated health effects.

Several other key questions and problems also must be considered when attempting to interpret the data reviewed in this document. While the epidemiology data provide strong support for the associations mentioned above, no credible supporting toxicologic data are yet available that provide insight into potential mechanisms. There is also a paucity of information of either a biological or clinical nature that argues for the biologic plausibility of the epidemiologic results. Nor is there much toxicologic data that elucidates the role of specific PM constituents in mediating responses of the type demonstrated by the epidemiologic analyses at low ambient PM concentrations. More specifically, although several hypotheses are discussed later with regard to possible mechanisms by which ambient PM may exert human health effects, little non-epidemiologic evidence is presently available to support or refute a causal relationship (i.e., to construct an exposure-dose-response continuum) between low ambient concentrations of PM and observed increased mortality or morbidity risks. Thus, specific causal agents cannot presently be confidently identified among typical ambient PM constituents, nor can mechanisms be clearly specified by which health effects of ambient PM are exerted.

Due to these uncertainties much caution is warranted with regard to derivation or extrapolation of quantitative estimates of increased risks for mortality or morbidity related to low level ambient PM exposures based on available epidemiology information.

13.4.1 Epidemiologic Evidence for Ambient PM Health Impacts

The health effects of short (24 h) and long-term (annual) PM exposure on mortality, hospitalization, respiratory symptom/illness, and pulmonary function change are examined across epidemiological, laboratory animal and controlled human studies. Where the information is available, the data for these health endpoints are also related to particle size, including PM_{10}, $PM_{2.5}$, and $PM_{(10-2.5)}$, as well as to specific chemical constituents such as $SO_4^=$ or H^+.

13.4.1.1 Ambient PM Mortality Effects

Early epidemiology studies of severe air pollution episodes in Europe and the U.S. from the 1930's to 1950's indicated that exposure to high ambient levels of urban air pollution can produce serious human health effects. By far, the most clearly defined health effects attributable to ambient PM exposure are the marked increases in daily deaths that occurred during episodes of high pollution (e.g., in the Meuse Valley in 1930, in Donora in 1948, and in London in 1952). During a London episode in the 1950s, for example, more than 4,000 excess deaths during a 4 to 5-day period were attributed to air pollution, with the greatest increase in death seen most clearly among patients over 45 years with lung and heart disease. The early episode studies demonstrated, as subsequently confirmed in several re-analyses, that primary and secondary particulate combustion products and sulfur oxide air pollution at sufficiently high concentrations (in excess of 500 to 1,000 $\mu g/m^3$ BS), exert lethal effects even though conclusively substantiated mechanisms of action underlying the observed episodic mortality have yet to be elucidated.

Recent studies in a variety of locations, summarized in Chapter 12, further implicate air pollution exposure in mortality at much lower ambient levels, including levels well below the current 24-h PM_{10} NAAQS of 150 $\mu g/m^3$ and annual PM_{10} NAAQS of 50 $\mu g/m^3$. More than 20 time-series analyses published in the late 1980s and early 1990s demonstrate significant positive associations between daily mortality and 24-h concentrations of ambient

particles indexed by various measures (black smoke, TSP, PM_{10}, $PM_{2.5}$, etc.) in numerous U.S. metropolitan areas and in other countries (e.g., Athens, São Paulo, Santiago). These studies collectively suggest that PM alone or in combination with other commonly occurring air pollutants (e.g., SO_2) is associated with daily mortality, the effect of PM appearing to be most constituent. In both the historic and recent studies, the association of air pollution exposure with mortality has been strongest in the elderly and for respiratory and cardiovascular causes of death. Furthermore, the recent analyses suggest a major role of PM relative to other air pollutants in terms of increased risk of mortality.

Time-series analyses strongly suggest a positive effect on daily mortality across the entire range of ambient PM levels. Relative risk (RR) estimates for daily mortality in relation to daily ambient PM concentration are consistently positive, and statistically significant (at $P \leq 0.05$), across a variety of statistical modeling approaches and methods of adjustment for effects of relevant covariates such as season, weather, and co-pollutants. Examination of Table 12-4 in Chapter 12 shows that relative risk estimates (RR) for non-accidental mortality in the total population associated with a 50 $\mu g/m^3$ increase in 24-h average PM_{10} range from 1.015 to 1.085. Relative risk estimates with PM_{10} as the only pollutant index in the model range from RR = 1.025 to 1.085, while the PM_{10} RR with multiple pollutants in the model range from 1.015 to 1.025. Higher relative risks are indicated for the elderly and for those with pre-existing respiratory conditions.

Mortality effects associated with chronic, long-term exposure to PM air pollution have been assessed in cross-sectional studies and more recently, in prospective cohort studies. A number of older cross-sectional studies provided indications of increased mortality associated with chronic (annual average) exposures to ambient PM (indexed mainly by TSP or sulfate measurements). However, unresolved questions regarding adequacy of statistical adjustments for other potentially important covariates (e.g., cigarette smoking, economic status, etc.) across cities tended to limit the degree of confidence that could be placed on such studies or on quantitative estimates of PM effects derived from them.

Several more recent studies, in contrast, have used subject-specific information about relevant covariates (such as cigarette smoking, occupational exposure, etc.), and appear to provide more reliable findings of long-term PM exposure effects. In particular, three new prospective cohort studies of mortality associated with chronic PM exposures were evaluated in

Chapter 12 as yielding especially useful information. The studies of California nonsmokers by Abbey et al. (1991) and Abbey (1994) found no significant mortality effects of previous TSP exposure in a small, young cohort. On the other hand, the larger and more extensive Harvard Six Cities (Dockery et al., 1993) and American Cancer Society (ACS) (Pope et al., 1995) studies agree in their findings of statistically significant positive associations between fine particles and excess mortality, although the ACS did not evaluate the contribution of other air pollutants. The RR estimates for total mortality in the Six-Cities study (with their 95 percent confidence intervals) per increments in PM indicator levels are as follows: the RR for 50 $\mu g/m^3$ PM_{15} is 1.42 (1.16, 2.01), the RR for 25 $\mu g/m^3$ $PM_{2.5}$ is 1.31 (1.11, 1.68), and the RR for 15 $\mu g/m^3$ SO_4 is 1.46 (1.16, 2.16). The estimates for total mortality derived from the ACS study are 1.17 (1.09, 1.26) for 25 $\mu g/m^3$ $PM_{2.5}$, and 1.10 (1.06, 1.16) for 15 $\mu g/m^3$ $SO_4^=$. In some cases, the life-long cumulative exposure of the study cohorts included distinctly higher past PM exposures, especially in the cities with historically higher PM concentrations; but more current PM measurements were used to estimate the chronic PM exposures. Thus, caution must be exercised regarding the use of the reported quantitative risk estimates, since somewhat lower risk estimates than the published ones are apt to apply. However, the chronic exposure studies, taken together, suggest that there may be increases in mortality in disease categories that are consistent with long-term exposure to airborne particles and that at least some fraction of these deaths reflect cumulative PM impacts above and beyond those exerted by acute exposure events.

The weight of epidemiologic evidence suggests that short-term ambient PM exposure likely contributes to increased daily mortality, and it also suggests that long-term PM exposure reduces survival time. It is extremely unlikely that study designs not yet employed, covariates not yet identified, or statistical techniques not yet developed could wholly negate the large and consistent body of epidemiologic evidence relating short-term PM exposure to daily mortality in U.S. urban areas. Similarly, although relatively few cohort studies of long-term PM exposure and mortality are available, they are consistent in direction and magnitude of excess risk with a larger body of cross-sectional annual mortality studies, and most show positive associations of PM exposure with mortality. In view of the consistency with which they are observed, it is unlikely that these associations could result entirely from important confounding factors as yet unidentified.

Variation in relative risks exists among the estimates for PM-related daily mortality. These estimates would be expected to vary if PM exposure truly affects daily mortality for the following reasons: (1) the toxicity of PM likely depends on its size distribution and chemical composition, and these characteristics differ among geographic areas; (2) local populations differ in demographic and socioeconomic characteristics; (3) the distribution of diseases differs among geographic locations; and (4) ambient PM means and ranges differ among geographic areas. Somewhat different RR estimates are therefore derived across varying PM ranges in different studies, even when they have been standardized to the same PM increment. This results in different site-specific RR estimates, as would be expected unless PM-mortality relationships are truly linear throughout the entire PM range and represent a general non-specific (i.e., chemical composition-independent) PM effect. On balance, the observed variations in RR estimates are not inconsistent with a real effect of PM exposure on daily mortality.

In many studies, daily mortality has been most strongly associated with PM levels occurring shortly (0 to 5 days) before death. These short intervals have been invoked as evidence that PM-induced mortality occurs primarily in persons who would have died soon, even without PM exposure. However, there is no pathophysiologic reason why the exposure-to-death interval need be related to the time by which the death itself is hastened. The existence of short exposure-to-mortality intervals neither requires nor excludes the possibility that at least a portion of PM-associated deaths are advanced by long time intervals. At the same time, available evidence does not allow confident quantitative inference as to PM-associated shortening of life.

Comparison of Size-Specific and Chemical-Specific Particle Effects on Mortality

An important objective of this chapter is to evaluate different exposure metrics based on size-specific and chemical-specific information. However, only a limited number of studies have included direct measurements of indicators of fine particle mass (i.e., $PM_{2.5}$, $PM_{2.1}$). Additional indirect support for fine particle effects is derived from studies that used BS, COH, KM, or sulfate measurements, which are primarily associated with components of fine particles. Information on chemical-specific PM constituents is limited to a few studies that included measures of particle strong acidity and/or sulfates; but the results of such analyses may best be

interpreted in terms of the exposure metrics being reflective of fine particle effects in general, rather than of acids or sulfates in particular.

Early indications that fine particles are likely important contributors to observed PM-mortality and morbidity effects came from evaluation of past serious air pollution episodes in Britain and the United States. The most severe episodes, as discussed in the 1982 Criteria Document (U.S. Environmental Protection Agency, 1982), were characterized by several consecutive days of very low wind speed conditions, during which large coarse mode particles rapidly settle out of the atmosphere and concentrations of fine mode particles dramatically increase. Even during non-episode conditions, mortality associations with BS or COH readings in Britain or the U.S. during the 1950s to 1970s most likely reflected contributions of fine mode particles. This is based on the low D_{50} cutpoints (≈ 4.5 μm) for the BS and COH methods described in Chapter 4, although some contribution of small inhalable particles (up to ~ 10 μm) cannot be entirely ruled out.

Table 13-3 summarizes effect estimates (relative risk information) derived from more recent epidemiology studies demonstrating health effects (mortality, morbidity) associations with ambient 24-h PM_{10} concentrations in U.S. and Canadian cities. The evidence summarized in Table 13-3 leaves little doubt that short-term PM_{10} concentrations typical of contemporary U.S. urban air sheds are correlated with detectable increases in risk of human mortality and morbidity. Less extensive evidence summarized in Table 13-4 also suggests that fine particles may be important contributors to the observed PM-health effects associations given the increased risks (of mortality, hospitalization, respiratory symptoms, etc.) associated with several different fine particle indicators (e.g., $PM_{2.5}$, $SO_4^=$, H^+).

Because of the potential impact of particle size on their observations, some investigators have attempted to determine what size and/or chemical form of particles had the strongest association with health effects. For example, in initial of data from St. Louis and eastern Tennessee (part of the Six-Cities Study), the strongest associations of daily mortality rates were seen with PM_{10} while progressively weaker associations were seen with $PM_{2.5}$, sulfate, and aerosol acidity (Dockery et al., 1992). However, because of the limited statistical power of the latter study and the lesser quantity of aerosol acidity data (only one year versus seven years for the other PM measures), the observation of weaker association of aerosol acidity with mortality is inconclusive.

TABLE 13-3. EFFECT ESTIMATES PER 50 $\mu g/m^3$ INCREASE IN 24-h PM_{10} CONCENTRATIONS FROM U.S. AND CANADIAN STUDIES

Study Location	RR (± CI) Only PM in Model	RR (± CI) Other Pollutants in Model	Reported PM_{10} Levels Mean (Min/Max)[†]
Increased Total Acute Mortality			
Six Cities[a]		—	
Portage, WI	1.04 (0.98, 1.09)	—	18 (±11.7)
Boston, MA	1.06 (1.04, 1.09)	—	24 (±12.8)
Topeka, KS	0.98 (0.90, 1.05)	—	27 (±16.1)
St. Louis, MO	1.03 (1.00, 1.05)	—	31 (±16.2)
Kingston/Knoxville, TN	1.05 (1.00, 1.09)	—	32 (±14.5)
Steubenville, OH	1.05 (1.00, 1.08)	—	46 (±32.3)
St. Louis, MO[c]	1.08 (1.01, 1.12)	1.06 (0.98, 1.15)	28 (1/97)
Kingston, TN[c]	1.09 (0.94, 1.25)	1.09 (0.94, 1.26	30 (4/67)
Chicago, IL[h]	1.04 (1.00, 1.08)	—	37 (4/365)
Chicago, IL[g]	1.03 (1.02, 1.04)	1.02 (1.01, 1.04)	38 (NR/128)
Utah Valley, UT[b]	1.08 (1.05, 1.11)	1.19 (0.96, 1.47)	47 (11/297)
Birmingham, AL[d]	1.05 (1.01, 1.10)	—	48 (21, 80)
Los Angeles, CA[f]	1.03 (1.00, 1.055)	1.02 (0.99, 1.036)	58(15/177)
Increased Hospital Admissions (for Elderly > 65 yrs.)			
Respiratory Disease			
Toronto, CAN[I]	1.23 (1.02, 1.43)[‡]	1.12 (0.88, 1.36)[‡]	30-39[*]
Tacoma, WA[J]	1.10 (1.03, 1.17)	1.11 (1.02, 1.20)	37 (14, 67)
New Haven, CT[J]	1.06 (1.00, 1.13)	1.07 (1.01, 1.14)	41 (19, 67)
Cleveland, OH[K]	1.06 (1.00, 1.11)	—	43 (19, 72)
Spokane, WA[L]	1.08 (1.04, 1.14)	—	46 (16, 83)
COPD			
Minneapolis, MN[N]	1.25 (1.10, 1.44)	—	36 (18, 58)
Birmingham, AL[M]	1.13 (1.04, 1.22)	—	45 (19, 77)
Spokane, WA[L]	1.17 (1.08, 1.27)	—	46 (16, 83)
Detroit, MI[O]	1.10 (1.02, 1.17)	—	48 (22, 82)

TABLE 13-3 (cont'd). EFFECT ESTIMATES PER 50 $\mu g/m^3$ INCREASE IN 24-h PM_{10} CONCENTRATIONS FROM U.S. AND CANADIAN STUDIES

Study Location	RR (± CI) Only PM in Model	RR (± CI) Other Pollutants in Model	Reported PM_{10} Levels Mean (Min/Max)[†]
Pneumonia			
Minneapolis, MN[N]	1.08 (1.01, 1.15)	—	36 (18,58)
Birmingham, AL[M]	1.09 (1.03, 1.15)	—	45 (19, 77)
Spokane, WA[L]	1.06 (0.98, 1.13)	—	46 (16, 83)
Detroit, MI[O]	—	1.06 (1.02, 1.10)	48 (22, 82)
Ischemic HD			
Detroit, MI[P]	1.02 (1.01, 1.03)	1.02 (1.00, 1.03)	48 (22, 82)
Increased Respiratory Symptoms			
Lower Respiratory			
Six Cities[Q]	2.03 (1.36, 3.04)	Similar RR	30 (13,53)
Utah Valley, UT[R]	1.28 (1.06, 1.56)[τ]	—	46 (11/195)
	1.01 (0.81, 1.27)[π]		
Utah Valley, UT[S]	1.27 (1.08, 1.49)	—	76 (7/251)
Cough			
Denver, CO[X]	1.09 (0.57, 2.10)	—	22 (0.5/73)
Six Cities[Q]	1.51 (1.12, 2.05)	Similar RR	30 (13, 53)
Utah Valley, UT[S]	1.29 (1.12, 1.48)	—	76 (7/251)
Decrease in Lung Function			
Utah Valley, UT[R]	55 (24, 86)[**]	—	46 (11/195)
Utah Valley, UT[S]	30 (10, 50)[**]	—	76 (7/251)
Utah Valley, UT[W]	29 (7,51)[***]	—	55 (1,181)

References:

[a]Schwartz et al. (1996a).
[b]Pope et al. (1992, 1994)/O_3.
[c]Dockery et al. (1992)/O_3.
[d]Schwartz (1993).
[g]Ito and Thurston (1996)/O_3.
[f]Kinney et al. (1995)/O_3, CO.
[h]Styer et al. (1995).
[I]Thurston et al. (1994)/O_3.
[J]Schwartz (1995)/SO_2.
[K]Schwartz et al. (1996b).
[L]Schwartz (1996).
[M]Schwartz (1994e).
[N]Schwartz (1994f).
[O]Schwartz (1994d).
[Q]Schwartz et al. (1994).
[P]Schwartz and Morris (1995)/O_3, CO, SO_2.
[R]Pope et al. (1991).
[S]Pope and Dockery (1992).
[T]Schwartz (1994g)
[W]Pope and Kanner (1993).
[X]Ostro et al. (1991)
[†]Min/Max 24-h PM_{10} in parentheses unless noted otherwise as standard deviation (± S.D), 10 and 90 percentile (10, 90). NR = not reported.
[τ]Children.
[π]Asthmatic children and adults.
[*]Means of several cities.
[**]PEFR decrease in ml/sec.
[***]FEV_1 decrease.
[‡]RR refers to total population, not just>65 years.

TABLE 13-4. EFFECT ESTIMATES PER VARIABLE INCREMENTS IN 24-h CONCENTRATIONS OF FINE PARTICLE INDICATORS ($PM_{2.5}$, $SO_4^=$, H^+) FROM U.S. AND CANADIAN STUDIES

Acute Mortality	Indicator	RR (± CI) per 25 $\mu g/m^3$ PM Increase	Reported PM Levels Mean (Min/Max)[†]
Six City[A]			
Portage, WI	$PM_{2.5}$	1.030 (0.993, 1.071)	11.2 (±7.8)
Topeka, KS	$PM_{2.5}$	1.020 (0.951, 1.092)	12.2 (±7.4)
Boston, MA	$PM_{2.5}$	1.056 (1.038, 1.0711)	15.7 (±9.2)
St. Louis, MO	$PM_{2.5}$	1.028 (1.010, 1.043)	18.7 (±10.5)
Kingston/Knoxville, TN	$PM_{2.5}$	1.035 (1.005, 1.066)	20.8 (±9.6)
Steubenville, OH	$PM_{2.5}$	1.025 (0.998, 1.053)	29.6 (±21.9)
Increased Hospitalization			
Ontario, CAN[B]	$SO_4^=$	1.03 (1.02, 1.04)	R = 3.1-8.2
Ontario, CAN[C]	$SO_4^=$	1.03 (1.02, 1.04)	R = 2.0-7.7
	O_3	1.03 (1.02, 1.05)	
NYC/Buffalo, NY[D]	$SO_4^=$	1.05 (1.01, 1.10)	NR
Toronto[D]	H^+ ($Nmol/m^3$)	1.16 (1.03, 1.30)[*]	28.8 (NR/391)
	$SO_4^=$	1.12 (1.00, 1.24)	7.6 (NR, 48.7)
	$PM_{2.5}$	1.15 (1.02, 1.78)	18.6 (NR, 66.0)
Increased Respiratory Symptoms			
Southern California[F]	$SO_4^=$	1.48 (1.14, 1.91)	R = 2-37
Six Cities[G]	$PM_{2.5}$	1.19 (1.01, 1.42)[**]	18.0 (7.2, 37)[***]
(Cough)	$PM_{2.5}$ Sulfur	1.23 (0.95, 1.59)[**]	2.5 (3.1, 61)[***]
	H^+	1.06 (0.87, 1.29)[**]	18.1 (0.8, 5.9)[***]
Six Cities[G]	$PM_{2.5}$	1.44 (1.15-1.82)[**]	18.0 (7.2, 37)[***]
(Lower Resp. Symp.)	$PM_{2.5}$ Sulfur	1.82 (1.28-2.59)[**]	2.5 (0.8, 5.9)[***]
	H^+	1.05 (0.25-1.30)[**]	18.1 (3.1, 61)[***]
Decreased Lung Function			
Uniontown, PA[E]	$PM_{2.5}$	PEFR 23.1 (-0.3, 36.9) (per 25 $\mu g/m^3$)	25/88 (NR/88)

References:
[A]Schwartz et al. (1996a)
[B]Burnett et al. (1994)
[C]Burnett et al. (1995) O_3
[D]Thurston et al. (1992, 1994)
[E]Neas et al. (1995)
[F]Ostro et al. (1993)
[G]Schwartz et al. (1994)

[†]Min/Max 24-h PM indicator level shown in parentheses unless otherwise noted as (± S.D.), 10 and 90 percentile (10,90) or R = range of values from min-max, no mean value reported.
[*]Change per 100 $nmoles/m^3$
[**]Change per 20 $\mu g/m^3$ for $PM_{2.5}$; per 5 $\mu g/m^3$ for $PM_{2.5}$ sulfur; per 25 $nmoles/m^3$ for H^+.
[***]50th percentile value (10,90 percentile)

More recent reanalyses of the Harvard Six-City Study by Schwartz et al. (1996a) examined the effects on daily mortality of 24-h concentrations of fine particles ($PM_{2.5}$), inhalable particles ($PM_{15/10}$), or coarse fraction particles ($PM_{15/10}$ minus $PM_{2.5}$) as exposure indices. Note that inhalable particles are denoted here by $PM_{15/10}$ to reflect the change from the use of PM_{15} cut point dichotomous samplers to PM_{10} cut point samplers for later years of the study. The results were transformed to standard increments of 25 µg/m^3 $PM_{2.5}$, 50 µg/m^3 $PM_{15/10}$, and 25 µg/m^3 for the coarse fraction ($PM_{15/10-2.5}$) and are graphically depicted in Chapter 12, Figure 12-33. Of the three PM indices, $PM_{2.5}$ had the highest RR for daily mortality across the six cities. The only exception was for Steubenville, where a statistically significant coarse particle effect was found (although the fine particle effect size was as large as in most other cities and the fine and coarse particle concentrations were highly correlated in Steubenville). The acid aerosol relationships were weaker than were fine particle relationships, possibly because the acid aerosol time series were much shorter than the PM time series, as noted above.

In spite of differences in climate and demographics, the results showed that there were similar increases in daily mortality associated with fine particles in all six cities, with RR ranging from 1.020 to 1.056 per 25 μg/m^3 $PM_{2.5}$. The results were statistically highly significant in Harriman-Kingston, St. Louis, Watertown, nearly so in Portage and Steubenville, but less so in Topeka where the fine particle concentrations were low. The excess risk of death by ischemic heart disease associated with $PM_{2.5}$ was about 40% higher than for all-cause nonexternal mortality. For death due to pneumonia or due to COPD the excess risk was more than twice as high as for other causes. Only Steubenville, which had an RR = 1.061 per 25 μg/m^3 coarse-mode particles, showed results suggestive of possible excess risk from coarse particles. Overall, these analyses suggest that, in general, the association between excess mortality and thoracic particles appears to be stronger for the fine than the coarse fraction.

When data for all six cities were combined, the estimate of the effects of $PM_{15/10}$ and $PM_{2.5}$ were even more significant, with $PM_{2.5}$ having a higher associated risk than $PM_{15/10}$. The combined estimate for coarse mode particles ($PM_{15/10}$-$PM_{2.5}$), on the other hand, was only marginally significant. The combined effects estimates derived for the sulfate component was a statistically significant predictor of excess mortality (although less so than either $PM_{15/10}$ or $PM_{2.5}$), but H^+ was not statistically significant, even with 1,183 days of data in four cities. These results do not necessarily implicate sulfates as the key fine particle component associated with

mortality effects; rather, sulfates may represent a surrogate index for fine particles in general. Other studies in areas with low sulfate levels suggest that increased risk is also associated with non-sulfate fine particle components.

Relationships between chronic (annual average) PM exposures (Dockery et al., 1993) indexed by different particle size indicators (PM_{15}, $PM_{2.5}$, PM_{15} to $PM_{2.5}$) and mortality effects as observed in the Harvard Six City Study were depicted graphically in Figure 12-8 of Chapter 12, emphasizing that there tends to be an increasing correlation of long-term mortality with PM indicators as they become more reflective of fine particle levels. These results are summarized in Table 13-5, along with findings from other key studies of U.S. and Canadian cities demonstrating associations between increased risk of mortality/morbidity and chronic (annual average) exposures to PM_{10} or fine particle indicators in contemporary North American urban air sheds.

The effect estimate results for the studies in Table 13-3 are characterized in terms of relative risks (RR) corresponding to a specific PM increment (50 $\mu g/m^3$ PM_{10}) that generally encompass the range of the data within each study. As seen in Table 13-3, the mean 24-h PM_{10} concentrations that were present during the studies generally ranged from 18 to 76 $\mu g/m^3$, with many of the highest daily values exceeding 100 $\mu g/m^3$. An indication of the potential for the occurrences of changes/increases of 24-h PM_{10} levels of the magnitude of 50 $\mu g/m^3$ can be drawn from a data set of three years of daily levels of PM_{10} in Philadelphia. During this study, the mean day-to-day differences seen in PM_{10} concentration was 8.6 $\mu g/m^3$ with a maximum day-to-day variation of 50.4 $\mu g/m^3$. Maximum daily values by season were: summer - 82 $\mu g/m^3$; winter - 77.5 $\mu g/m^3$; spring - 54.7 $\mu g/m^3$; and fall - 54.4 $\mu g/m^3$. The difference between the median and maximum value for summer was 54.4 $\mu g/m^3$ and for winter, 58.3 $\mu g/m^3$.

Acid Aerosol Mortality Effects

Several epidemiologic studies have measured the mass of acidic aerosols or sulfates. This acid aerosol mass would primarily be found in the fine PM fraction, that is in ambient fractions < $PM_{2.5}$. Studies of past episodes suggest that there can be both acute and chronic

TABLE 13-5. EFFECT ESTIMATES PER INCREMENTS[a] IN ANNUAL MEAN LEVELS OF FINE PARTICLE INDICATORS FROM U.S. AND CANADIAN STUDIES

Type of Health Effect & Location	Indicator	Change in Health Indicator per Increment in PM[a]	Range of City PM Levels Means ($\mu g/m^3$)
Increased total chronic mortality in adults		Relative Risk (95% CI)	
Six City[b]	$PM_{15/10}$	1.42 (1.16-2.01)	18-47
	$PM_{2.5}$	1.31 (1.11-1.68)	11-30
	$SO_4^=$	1.46 (1.16-2.16)	5-13
ACS Study[c] (151 U.S. SMSA)	$PM_{2.5}$	1.17 (1.09-1.26)	9-34
	$SO_4^=$	1.10 (1.06-1.16)	4-24
Increased bronchitis in children		Odds Ratio (95% CI)	
Six City[d]	$PM_{15/10}$	3.26 (1.13, 10.28)	20-59
Six City[e]	TSP	2.80 (1.17, 7.03)	39-114
24 City[f]	H^+	2.65 (1.22, 5.74)	6.2-41.0
24 City[f]	$SO_4^=$	3.02 (1.28, 7.03)	18.1-67.3
24 City[f]	$PM_{2.1}$	1.97 (0.85, 4.51)	9.1-17.3
24 City[f]	PM_{10}	3.29 (0.81, 13.62)	22.0-28.6
Southern California[g]	$SO_4^=$	1.39 (0.99, 1.92)	—
Decreased lung function in children			
Six City[d,h]	$PM_{15/10}$	NS Changes	20-59
Six City[e]	TSP	NS Changes	39-114
24 City[i,j]	H^+ (52 nmoles/m^3)	−3.45% (-4.87, -2.01) FVC	—
24 City[i]	$PM_{2.1}$ (15 $\mu g/m^3$)	−3.21% (-4.98, -1.41) FVC	—
24 City[i]	$SO_4^=$ (7 $\mu g/m^3$)	−3.06% (-4.50, -1.60) FVC	—
24 City[i]	PM_{10} (17 $\mu g/m^3$)	−2.42% (-4.30, -.0.51) FVC	—

[a]Estimates calculated annual-average PM increments assume: a 100 $\mu g/m^3$ increase for TSP; a 50 $\mu g/m^3$ increase for PM_{10} and PM_{15}; a 25 $\mu g/m^3$ increase for $PM_{2.5}$; and a 15 $\mu g/m^3$ increase for $SO_4^=$, except where noted otherwise; a 100 nmole/m^3 increase for H^+.
[b]Dockery et al. (1993)
[c]Pope et al. (1995)
[d]Dockery et al. (1989)
[e]Ware et al. (1986)
[f]Dockery et al. (1996)
[g]Abbey et al. (1995a,b,c)
[h]NS Changes = No significant changes.
[i]Raizenne et al. (1996)
[j]Pollutant data same as for Dockery et al. (1996)

health effects of strongly acidic PM. Studies of historical pollution episodes, notably the London Fog episodes of the 1950's and early 1960's, indicate that acute exposures to extreme elevations of 24-h acid aerosol concentrations may be associated with excess daily human mortality when present at times of elevated concentrations of BS and SO_2. In addition, significant associations were found between acid aerosols ($\leq$ 30 $\mu g/m^3$ as H_2SO_4, 24-h or $\leq \sim$600 nmoles/m^3 H^+, 24-h) and mortality in London during non-episode pollution periods of the 1960s and 1970s, though these associations could not be separated from those for BS or SO_2. Studies evaluating present-day U.S. levels of acidic aerosols have not found associations between acid aerosols and acute and chronic mortality, but the series of H^+ data used may not have been long enough to detect H^+ associations.

Based on laboratory animal toxicology studies, it is known that sulfuric acid aerosols exert their action throughout the respiratory tract, with the site of deposition dependent upon particle size and the response dependent on mass and number concentration at specific deposition sites. At very high concentrations that are not environmentally realistic, mortality can occur in toxicological studies following acute exposure, due primarily to laryngospasm or bronchoconstriction; larger acidic particles may be somewhat more potent in this regard than smaller ones. As seen in these studies, extensive pulmonary damage, including edema, hemorrhage, epithelial desquamation, and atelectasis can also cause death, but even in the most sensitive animal species, lethal concentrations are at least a thousand-fold greater than current ambient levels.

The available laboratory animal findings regarding acid aerosols provide no evidence that ambient acidic PM components contribute to mortality and essentially no quantitative guidance as to the ambient PM levels at which mortality would be expected to occur in either healthy or diseased humans. The laboratory animal effects were observed at acid levels that exceed worst-case ambient concentrations by more than ten-fold. Also, since the inhalable particle size range for common laboratory animals is generally < 2 to 4 μm, only comparisons between inhalable and ultrafine particles were possible. There were no obvious differences between responses of laboratory animals exposed to ultrafine acid aerosol as compared to larger inhalable acidic aerosols (see Section 13.6.7).

Shortening of Life Associated with Ambient PM Exposure

The public health burden of ambient PM-mediated mortality depends on both the number of deaths and the shortening of life that PM exposure causes or promotes. Knowledge of the true excess mortality and prematurity of death attributable to PM would be valuable to environmental risk managers and scientists in predicting and monitoring the public health benefit of reducing ambient PM exposure.

Epidemiologic findings suggest that short-term ambient PM exposure can trigger terminal events. Also, long-term PM exposure could conceivably promote life-shortening chronic illness. The relative risk ratios derived from long-term U.S. cohort studies of PM exposure and mortality are considerably larger than those from daily mortality studies. This suggests that a portion of deaths associated with long-term PM exposure may be independent of the daily deaths associated with short-term exposure and/or that some factor not accounted for may be contributing to these effects. In both long-term and short-term studies, the PM associations with mortality are strongest in the elderly for respiratory and cardiovascular causes of death.

Available experimental evidence provides only minimal biological understanding of PM's true role in influencing mortality. At the same time, several general pathways by which long-term and short-term PM exposure might plausibly increase mortality have been postulated. For example, long-term PM exposure might promote life-shortening chronic respiratory illness, the terminal event of which could be infection or other insult unrelated to recent PM exposure. Conversely, episodic short-term PM exposure might trigger death in highly susceptible persons with preexisting severe illnesses unrelated to long-term PM exposure. Or, in some individuals, ambient PM exposures might both promote chronic illness and trigger death. Emerging experimental evidence indicates that all of these should be considered as possibilities.

Confident quantitative determination of years of life lost to ambient PM exposure is not yet possible; life shortening may range from days to years. Two recent epidemiologic analyses (Spix et al., 1993; Cifuentes and Lave, 1996) suggest that some portion of PM-induced daily mortality occurs in people who are already so ill that they would soon die even without PM exposure. In addition to non-episodic increase in PM-related mortality, Cifuentes and Lave estimate that 37 to 87% of the adult deaths occurring during identifiable short-term PM episodes may be premature by only a few days. The public health implications of this estimate are not yet clear because the proportion of all PM-associated daily deaths occurring during episodes, and the

strengths of PM-daily mortality relationships during episodes relative to other periods, have not been determined.

The upper limit of PM-associated life shortening is not known and will also be difficult to determine. Available evidence regarding the effect of smoking on mortality may be of some contextual use in estimating this limit. Davis and Novotny (1989) investigated smoking-attributable mortality and years of life lost to smoking in chronic obstructive pulmonary disease (COPD). They reported that, in 1984, 51,013 (79.4%) of a calculated total of 64,211 COPD deaths in the U.S. were attributable to smoking and that 82% of these deaths occurred in persons aged at least 65 years. These smoking-attributable deaths represented a total of 501,290 years of life lost in relation to average life expectancy. These figures yield an average of 9.8 years of life lost per smoking-attributable COPD death. It is highly unlikely that PM-attributable life shortening would approach or exceed this average at current ambient U.S. PM levels. Nevertheless, life shortening could conceivably be on the order of years, especially if smoking and PM exposure exert synergistic long-term effects in COPD.

In summary, most available epidemiologic evidence suggests that increased mortality results from both short-term and long-term ambient PM exposure. Limitations of available evidence prevent quantification of years of life lost to such mortality in the population. Life shortening, lag time, and latent period of PM-mediated mortality are almost certainly distributed over long time periods, although these temporal distributions have not been characterized. Increased biological understanding of PM's role in relevant mechanisms is essential to guide further epidemiologic study of these complex issues.

13.4.1.2 Ambient PM Morbidity Effects

Consistent with the above-noted observations of PM-induced mortality effects, numerous epidemiologic studies in the U.S. and elsewhere have demonstrated significant associations between ambient PM exposures indexed by a variety of indicators (BS, TSP, PM_{10}, $PM_{2.5}$, sulfates, etc.) and various acute and chronic morbidity outcomes. Such outcomes include, for example, hospital admissions, increased respiratory symptoms, and decreased lung function. Tables 13-3 to 13-5 provide effect estimates for various PM indicators drawn from recent U.S. and Canadian studies thought to provide reasonably credible quantitative estimates that are likely

representative of the range of increased mortality and morbidity risks associated with ambient exposures to PM in contemporary U.S. urban air sheds.

Hospitalization and Outpatient Visits

Potentially, the most severe morbidity measure evaluated with regard to PM exposure is hospitalization with a cardiopulmonary diagnosis. This outcome is relevant to the PM-mortality relationships discussed above. Some morbidity outcomes require hospitalization immediately, while others may require several days of progression to end in an admission. Exposure-response lag periods are not yet well examined for hospital admissions related to PM exposures.

Both COPD and pneumonia hospitalization studies show moderate but statistically significant relative risks in the range of 1.06 to 1.25 resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent. There is a suggestion of a relationship between ambient PM_{10} and heart disease admissions, but the estimated effects are smaller than those for other endpoints (see Figure 12-1 in Chapter 12). While a substantial number of hospitalizations for respiratory illnesses occur in those $\geq$65 years of age, there are also numerous hospitalizations for those under 65 years of age. Several of the hospitalization studies restricted their analysis by age of the individuals, but did not explicitly examine younger age groups. One exception was Pope (1991) who reported an increase in hospitalization for Utah Valley children (aged 0 to 5) for monthly numbers of admissions in relation to PM_{10} monthly averages, as opposed to daily admissions in relation to daily PM levels used in other studies.

Studies examining associations between other indicators of fine particles, e.g., British smoke (BS), or indicators of total particle concentrations (TSP) and hospital admissions also report finding significant relationships. One study in Spain, for example, found a statistically significant association between changes in hospital admissions and BS during the winter season. Also, in Finland, TSP was found to be significantly correlated with hospitalization admissions for asthma. For those age 65 or older in Philadelphia, hospitalization for pneumonia showed a RR at about 1.22 (1.10 to 1.36) corresponding to an increase of 100 $\mu g/m^3$ of TSP.

Increased hospital admissions for respiratory causes documented during the 1952 London Fog episode suggested an association with sulfuric acid aerosols as well as with BS and SO_2 measurements. More recent studies have shown a consistent relationship between summertime levels of both sulfates and O_3 with hospital admissions. Two Canadian studies estimated a 3 to

4% increase in annual respiratory hospital admissions for about a 13 to 14 $\mu g/m^3$ increase in concentration of the sulfate fraction. A corresponding 2 to 3% increase in cardiac admissions was reported in one of these studies. While sulfates have been predictive of health effects in some studies, it is not clear whether the sulfate-related effects can be attributed to their acidity or other characteristics, or if they are more broadly related to fine particles in general. Another study found associations between ambient acidic aerosols and summertime respiratory hospital admissions both in New York State and Toronto, Canada, even after controlling for potentially confounding temperature effects. In the Toronto analysis, the increase in respiratory hospital admissions associated with H^+ was roughly six times that for non-acidic PM_{10} (per unit mass). In these analyses H^+ effects were estimated to be the largest during acid aerosol episodes (days) ($H^+ \geq 10$ $\mu g/m^3$ as H_2SO_4, or $\approx$200 nmoles/m^3 H^+), which occur roughly 2 to 3 times per year in eastern North America. Sulfate concentrations that were previously found to be correlated with respiratory admissions are associated with acidic aerosols in Eastern North America. In these recent analyses, the H^+ associations with respiratory hospital admissions were found to be stronger than for sulfates or any other PM component monitored. This Toronto study showed no associations for PM_{10}-$PM_{2.5}$ or for TSP-PM_{10} measures of coarse particles. Other studies, which did not directly measure coarse particles, have evaluated situations where PM was dominated by coarse particles. Gordian et al. (1996) reported increased outpatient visits for asthma and upper respiratory illness, but not for bronchitis in Anchorage, Alaska where PM_{10} contains primarily coarse particle-crustal material and volcanic ash. Hefflin et al. (1994) determined that the maximum observed/expected ratio was 1.2 for respiratory disorders resulting from dust storms on October 16 and 21, 1991 which produced the highest PM_{10} levels of 1991 (i.e., 1,689 and 1,035 $\mu g/m^3$, respectively) in southeast Washington state. PM_{10} was considered to be mostly from natural sources as compared to industry or combustion sources. In both of these studies, numerous marked exceedances of the PM_{10} standards occurred.

Community-Based Respiratory Illness and Pulmonary Function Studies

Acute respiratory illness studies may include several different endpoints, but typically present results for: (1) upper respiratory illness, (2) lower respiratory illness, or (3) cough (as summarized earlier in Chapter 12, Figure 12-5). The studies of upper respiratory illness do not show a consistent relationship with PM, although some of this inconsistency could be explained

by the differences in populations studied. The studies of lower respiratory disease, however, yielded odds ratios (OR) which ranged from 1.10 to 1.28, and studies of cough gave odds ratios ranging from 0.98 to 1.29 (note that the odds ratios were estimated for a 50 $\mu g/m^3$ increase in PM_{10} or its equivalent). An exception in each of the latter two categories was the Six City study which produced ORs of 2.0 and 1.51 for lower respiratory disease and cough, respectively. These three respiratory illness endpoints had similar general patterns of results. The odds ratios were generally positive, the 95% confidence intervals for about half of the studies were statistically significant (i.e., the lower bound exceeded 1.0) and, for each endpoint, one study had a high odds ratio. Limited data were available relating PM exposure to asthma or respiratory symptoms in adults.

As part of the Six Cities studies, three analyses done for different time periods suggest a chronic effect of PM exposure on respiratory disease. Chronic cough, chest illness, and bronchitis showed positive associations with PM for the earlier surveys. A recent study is strongly suggestive of an effect on bronchitis from acidic particles or from other PM.

Pulmonary function studies (summarized in Chapter 12, Figure 12-6) are suggestive of short term effects resulting from particulate exposure. Peak expiratory flow rates show decreases in the range of 2 to 5 l/min resulting from an increase of 50 $\mu g/m^3$ in PM_{10} or its equivalent, with somewhat larger effects in symptomatic groups such as asthmatics. Studies using FEV_1 or FVC as endpoints show less consistent effects. For comparison, a passive smoking study of over 16,000 children found that maternal smoking decreased a child's FEV_1 by 10 to 30 ml. An estimate of the effect of PM on pulmonary function in adults found a 29 (±10) ml decrease in FEV_1 per 50 $\mu g/m^3$ increase in PM_{10}, which is similar in magnitude to the changes found in children, although a smaller percent change.

The chronic pulmonary function studies are less numerous than the acute studies and the results are inconclusive. The Six-City studies, which had good monitoring data, showed no associations of chronic pulmonary function effects with long-term particulate pollution measurements. Other studies found small, but statistically significant, decreases in FVC in healthy non-smokers or other pulmonary function effects that may be attributed to either acidic particles or PM in general. The absence of a strong association between chronic pulmonary function changes and PM calls into question the viability of one of the hypothetical mechanisms

for chronic PM-mortality relationships, namely the acceleration of the age-related decline in pulmonary function.

In addition to respiratory symptoms, bronchitis prevalence rates reported in the Six-City study were found to be more closely associated with annual average H^+ concentrations than with PM in general. As mentioned earlier, in a study of children in 24 U.S. and Canadian communities, bronchitis symptoms were shown to be significantly associated with strongly acidic PM. Thus, chronic exposures to strongly acidic PM may have effects on measures of respiratory health in children. The acid levels were highly correlated to other fine particle indicators such as $PM_{2.1}$, as noted previously.

Overall, the morbidity studies qualitatively indicate that acute PM exposures are associated with hospital admission for respiratory disease, increased occurrence of respiratory disease symptoms, and pulmonary function decrements. As stated above, hospitalization studies and acute pulmonary function changes suggest quantitative relationships. Also, some limited evidence exists for association of ambient acidic aerosol exposures with increased acute or chronic respiratory symptoms.

Comparison of PM_{10} Versus $PM_{2.5}$ Exposure Effects on Morbidity

Dosimetry models predict that total deposition of fine mode particles in the alveolar region of the lower respiratory tract (alveoli, terminal bronchioles) is somewhat greater than in the tracheobronchial region. It is therefore important to consider whether exposure indices for the fine fraction (e.g., $PM_{2.5}$) show larger and more significant effects than indices that also include coarse particles (e.g., PM_{10}), which may have a greater deposition efficiency in the larger and more proximal airways. Mechanistic effects caused by PM in these different lower respiratory tract regions may be different, potentially leading to different health outcomes. While numerous studies of PM related respiratory morbidity have been conducted using PM_{10} as an indicator, only limited numbers of studies have examined the effects of fine particle indicators such as $PM_{2.5}$. Obviously, the only meaningful direct comparison of the effect of PM_{10} to $PM_{2.5}$ is provided when a study includes both exposure measures and evaluates effects in relation to the coarse fraction $PM_{(10-2.5)}$ as well. PM_{10} was a better predictor of respiratory disease in the Six-City study, whereas $PM_{2.5}$ was a better predictor of pulmonary function effects in Tucson, where coarse particles likely represent a larger fraction of PM_{10} than in eastern U.S. cities. Other

studies using $PM_{2.5}$ to evaluate acute morbidity have not provided information that permits assessment of these two exposure indices with regard to health outcomes.

Two more recent chronic exposure studies permit comparison of results for PM_{10}, $PM_{2.1}$, and particulate acidity. Children living in communities with the highest levels of particle strong acidity were more likely (OR = 1.66, 95% CI = 1.11, 2.48) to report at least one episode of bronchitis in the past year compared to children living in communities with the lowest levels of acidity. The odds ratios for bronchitis were similar at 1.50 (increment of 15 $\mu g/m^3$; 95% CI = 0.91, 2.47) for $PM_{2.1}$ and 1.50 (increment of 17 $\mu g/m^3$; 95% CI = 0.93 to 2.43) for PM_{10}, respectively. No other respiratory symptoms, including asthma symptoms, were significantly associated with any of the pollutants. The strong correlations between several of the pollutants in this study, especially particle strong acidity with sulfate (r = 0.90) and $PM_{2.1}$ (r = 0.82), make it difficult to distinguish the agent of most interest.

In children, a 52 nmole/m^3 difference in annual mean particle strong acidity was associated with a 3.5% deficit in FVC (adjusted) and a 3.1% deficit in FEV_1 (adjusted) with a slightly larger deficit in lifelong residents of their communities. Slightly smaller deficits were seen using total sulfate, $PM_{2.1}$, and PM_{10} as pollutant exposure measures, and these deficits were also statistically significant.

These few studies on $PM_{2.5}$ show morbidity effects that are difficult to separate both from PM_{10} measures and acid aerosol measures discussed above. The $PM_{2.5}$ studies do show effects related to exposure to the fine fraction. However, high correlations among $PM_{2.5}$, PM_{10}, and acid aerosols make it very difficult to distinguish among these exposure indicators.

Other information suggests that coarse PM effects may warrant continued attention. There are epidemiological findings of physician visits for asthma associated with coarse crustal PM (e.g., Gordian et al., 1996). Also, therapeutic aerosols used in the treatment of asthma are generally in a size range from 2.5 to 5 μm, although greatest penetration into the lung is with the particles at the lower end of this range (i.e., 2.5 to 3.0 μm) (Kim et al., 1985). Thus, particles in the coarse fraction of PM_{10} appear to be associated with the exacerbation of asthma via ambient exposure, and analogous sized aerosols are used in the treatment of asthma via metered-dose inhalers.

13.4.2 Assessment of Validity and Coherence of Epidemiologic Findings

13.4.2.1 Human Exposure Assessment: Uncertainties and Implications

To varying extents, all available epidemiologic studies are subject to uncertainty in assessment of individual subjects' exposures to ambient PM and other air pollutants. Studies of PM are especially prone to such uncertainty because PM is physically and chemically far more complex than any other NAAQS pollutant. Such uncertainty tends to be greatest in hospitalization and mortality studies, because measurements from limited numbers of ambient monitoring stations have generally been applied to large populations in broad geographic areas, without adjustment for factors affecting individuals' indoor and personal exposures. Individual exposure estimates have seldom been made in available epidemiologic studies, and remain subject to much uncertainty even when available.

Even at fixed outdoor stations, accurate, thorough measurement of ambient PM size distributions and chemical constituents is technologically challenging and expensive. Ambient measurements are not yet available in sufficient accuracy or detail to enable thorough comparison of the potencies of specific constituents of the PM complex. For example, few direct measurements of $PM_{2.5}$ and inhalable coarse fraction PM, and no size-specific measurements of PM < 1.0 μm, are yet available for epidemiologic assessment. Similarly, beyond sulfates, nitrates, and to some extent H^+ and organic compounds, specific chemical components of PM have yet to be extensively epidemiologically assessed. Thus, for example, very little biomedical information has yet been analyzed against levels of the non-sulfate fraction of $PM_{2.5}$. Despite these limitations, several salient points appear to be emerging from assessment of currently available information.

For example, although generally useful for qualitative epidemiologic demonstration of PM effects, TSP measurements can include large coarse-mode particles that exceed the inhalable range. Thus, TSP can reasonably be expected to provide "noisy" estimates of exposure-effect relationships if such relationships are due to inhalable particle fractions of the measured TSP mass. PM_{10} is a better index of the inhalable particles than is TSP, and PM_{10} may be a better index of ambient fine particle exposure than TSP because the smaller particulate fraction contained in PM_{10} is more uniformly distributed in an urban area or region than are larger coarse particles also indexed by TSP.

As discussed in Section 13.2.6, $PM_{2.5}$ particles are generally likely to be more uniformly distributed than coarse particles within an urban airshed. For example, while PM_{10} levels vary from site to site, $PM_{2.5}$ levels have been shown to be particularly well correlated across at least one eastern metropolitan region, i.e., Philadelphia (Burton et al., 1996; Wilson and Suh, 1996). Also as noted earlier, fine particles are at least as likely to infiltrate indoors as are coarse particles, but the fine particles are removed less rapidly from indoor air than coarse particles. Thus, outdoor ambient fine particle concentrations may be better predictors of total human exposure to ambient fine particles than ambient coarse particle concentrations are of total exposure to ambient coarse particles.

Overall, then, it appears that size-specific fixed-station ambient PM measurements generally approximate total ambient fine PM exposure more closely than coarse PM exposure. Within the fine fraction, fixed-station measurements of ambient $SO_4^=$ likely approximate total exposure to sulfates better than similar measurements of H^+ would index total H^+ exposure, because a higher proportion of $SO_4^=$ persists indoors (H^+ is neutralized by indoor ammonia). Furthermore, because misclassification of exposure tends to bias toward the null hypothesis, the larger error in ambient coarse PM and H^+ estimates could produce more underestimation of effects of coarse than of fine PM, and of H^+ than of $SO_4^=$. On balance, available health effects estimates, whatever their magnitude and direction, are more subject to uncertainty for coarse than for fine PM, and for H^+ than $SO_4^=$.

Difficulties in distinguishing between possible differences in health effects from particles of various sizes and chemistries that fluctuate together also represent a limitation in interpreting existing long-term PM exposure studies. Cross-sectional and prospective cohort studies have reported significant mortality associations for fine particles, indexed by $PM_{2.5}$ (Dockery et al.,

1993) or sulfates (Ozkaynak and Thurston, 1987). However, significant PM/mortality associations have also been reported in areas where summertime sulfates are not the major component of PM (e.g., winter analysis of Santa Clara, CA; Los Angeles, CA).

13.4.2.2 Model Selection/Specification Issues

Model selection/specification issues assume many forms, including distributional assumptions, assumptions about temporal structure or correlation, assumptions about random and systematic components of variability, assumptions about the shape of the relationship between response and covariate, and assumptions about additivity and interactions of covariates. Most studies evaluate some of these model specification issues, but rarely provide enough information for the reader to independently assess the conclusions. Some of the model specification issues have been shown to have the potential for substantially modifying the conclusions reached by the analyses. The most sensitive model specification issues appear to be: adjustments for seasonality and for long-term time trends; adjustments for co-pollutants; and adjustments for weather variables. An in depth discussion of model specification for acute mortality studies, is presented in Section 12.6.2, where PM_{10} studies of mortality are reviewed and analyzed (Pope et al., 1992; Ostro et al., 1996; Dockery et al., 1992; Thurston and Kinney, 1995; Kinney et al., 1995; Ito et al., 1995; Styer et al., 1995). Also, importantly, alternative TSP mortality analyses for the same city, Philadelphia (Moolgavkar et al., 1995, Li and Roth, 1995; Wyzga and Lipfert, 1995; Cifuentes and Lave, 1996; Samet et al., 1995; Schwartz and Dockery, 1992b) are reviewed and analyzed.

Differences in model specification may produce important differences in estimates of PM effects. The general concordance of PM effects estimates, particularly in the analyses of short-term mortality studies, is a consequence of certain appropriate choices in modelling strategy that most investigators have adopted using several different types of standardized models (GLM, LOESS, etc.) and a variety of specific specifications. For example, in short-term studies of mortality or hospital admissions, it is important that large differences occurring over time be extracted before assessing short-term changes in health effects attributable to concurrent short-term changes in air pollution. However, several methods appear to be adequate for carrying out such adjustments, including nonparametric detrending, use of indicator variables for season and year, and (in older studies) filtering. The largely consistent specific results, indicative of

significant positive associations of ambient PM exposures and human mortality/morbidity effects, are not model-specific, nor are they artifactually derived due to misspecification of any specific model. The robustness of the results of different modelling strategies and approaches increases confidence in their validity.

13.4.2.3 Evaluation of Potential Influences Due to Weather

A variety of methods also appear to be capable of adequately adjusting time series data for the effects of weather. Most PM epidemiology studies use temperature and dewpoint as covariates, with several parametric models (possibly differing by season) and nonparametric smoothing models appearing to be adequate. Other weather variables, such as changes in barometric pressure, may also be predictive. Models that used synoptic weather categories as indicator variables, in which the categories were defined independently of information about the health effect, provide a plausible *a priori* basis for weather covariate adjustments as Pope and Kalkstein (1996) have shown for the Utah Valley study. At this time, relatively few studies have examined possible statistical interactions between weather and air pollution (Lipfert and Wyzga, 1995). While the role of weather-related variables is clearly important, this issue appears to have been adequately addressed in most of the recent studies reviewed in Chapter 12, and the relative insensitivity of PM coefficients to different methods of weather adjustment has been demonstrated in these studies including recently reported reanalyses of several data sets by HEI. While weather clearly affects human health, there does not seem to be much basis for believing that weather can explain a substantially greater part of the health effects attributed to PM than has already been accounted for by the empirical models used in the health studies assessed in Chapter 12.

13.4.2.4 Evaluation of Potential Influences of Co-pollutants

Other pollutants such as SO_2, O_3, and CO play a role in modifying the relationship between PM and mortality. When they are incorporated into models examining these relationships, the RR is usually smaller. Multi-pollutant models can cause differences in interpretation for a single-pollutant model such as when the correlation between PM and the other pollutants is sufficiently high that attributed health outcomes are shared among the pollutants. The most

poorly measured pollutant is usually the one that is driven toward no statistically significant estimate of effect.

Some of the studies cited in Chapter 12 include substantial assessments of the effect of potential confounding from co-pollutants. It was possible to carry out a statistical adjustment for co-pollutants in some studies, with the PM effect size estimated with and without the potential confounder in the model. The PM effect size estimates and their statistical uncertainty in many studies showed little sensitivity to the adjustment for co-pollutants. However, in some other analyses where was substantial confounding with co-pollutants such as SO_2 or O_3, estimates of RR for PM without inclusion of the confounders in the statistical concentration-effect model used in these studies were quantitatively similar to RR estimates from other studies where confounding was either avoided or was shown statistically to have little effect. This includes cases where PM effects were demonstrated in cities with very low levels of other major copollutants present, as well as in cities with moderate to high levels of one or another copollutant.

Some investigators have noted that similarity of PM regression coefficients in single and multi-pollutant models is sufficient to show that PM is not confounded by the other pollutants. When the RR estimates for PM are relatively unchanged and there is little increase in the width of the confidence interval, then one can say there is little evidence of confounding. For example, in the Utah Valley mortality study (Pope et al., 1992), the RR estimates for the summer season and the width of the confidence intervals for PM_{10} were similar whether the model did not include ozone, included daily average ozone, or used maximum daily 1-h ozone as the co-pollutant measure. The summer PM coefficient, with or without ozone, is similar to the winter value, when ozone levels were so low as to have little probable effect on mortality, which illustrates both covariate adjustment and confounder avoidance strategies in the same study.

The model for the Los Angeles mortality studies (Kinney et al., 1995) evaluated the results of including co-pollutants, O_3 and CO. Including O_3 in the model along with PM_{10}, did not change the RR for PM, but increased its uncertainty slightly so that the RR for PM was now only marginally significant. Including CO in the model reduced the RR for PM which was also less significant. Thus, the PM-mortality association was not completely separable from other copollutants. A sensitivity analysis by Schwartz and Dockery (1992b) for mortality in Steubenville indicates that including SO_2 reduced the TSP effect. However, the decrease was

small with RR for TSP only decreasing from 1.04 without including SO_2 to 1.03 per 100 $\mu g/m^3$ when SO_2 was included.

Most studies have provided very little empirical basis for the reader to assess the adequacy of the fitted model, especially for analyses involving copollutants. The HEI report (Samet et al., 1995) presents three-dimensional surfaces showing the smoothed or fitted mortality response versus TSP and SO_2 for the 1973 to 1980 Philadelphia data set. These analyses indicate that both TSP and SO_2 were associated with significant increases in mortality but there were important differences in effect depending on season and on the range of TSP or SO_2 values. There was a relationship between SO_2 and excess mortality at TSP concentrations below 75 $\mu g/m^3$, but the relationship was not evident at above 50 ppb SO_2 or above 75 to 100 $\mu g/m^3$ TSP concentration. Thus, it is clearly not correct to conclude from the additive linear model results that one pollutant is always (or never) a better predictor of excess mortality in Philadelphia than is the other pollutant. The Samet et al. (1995) analyses suggest that concluding from an additive linear model that inclusion of copollutants generally lowers the effect attributable to PM may not always apply to a more accurate nonparametric model.

Recent reanalyses of the Philadelphia mortality-TSP data (Moolgavkar et al., 1995b; Wyzga and Lipfert, 1995; Samet et al., 1995, 1996a; Cifuentes and Lave, 1996) have elucidated some of the complex issues relating to analyses of urban air pollution mixtures. The first point is that the relationship between mortality and different air polluitants may be different from season to season. This may be due, in part, to substantial seasonal differences in the correlation structure among the multiple pollutants in the urban airshed (Samet et al., 1996a, discussed in Section 12.6). Furthermore, there may be additional interactions within each season involving TSP and temperature (Wyzga and Lipfert, 1995), although a study of TSP and synoptic weather categories in Utah Valley found little evidence for interaction of PM_{10} and weather (Pope and Kalkstein, 1996).

Secondly, while some studies find that including O_3 in a model with TSP can modify the estimated TSP seasonal effect (Moolgavkar et al., 1995b), other studies find that O_3 has a significant additive effect on mortality that is largely unconfounded with the TSP or SO_2 effects (Cifuentes and Lave, 1996; Samet et al., 1996a). CO has little effect on mortality, as does NO_2 by itself, but including NO_2 in a model with either TSP and SO_2 tends to increase the effects of both (Samet et al., 1996a). While TSP, SO_2, NO_2, CO, and O_3 are modestly correlated in the

Philadelphia studies, these correlations are not so high as to preclude the possibility of identifying separate air pollutant effects in different seasons (discussed in Section 12.6).

Thirdly, the relationship between TSP, SO_2, and mortality may be intrinsically nonlinear (Samet et al., 1995; Cifuentes and Lave, 1996). The additive linear models used in most studies to assess effects of copollutants may therefore not be adequate to characterize the more complex nonlinear interrelationships among them.

Finally, the estimated TSP effects for Philadelphia are quantitatively similar to those in other studies. Estimates of effects using PM indicators in communities where SO_2 concentrations are low, such as Utah Valley, are also similar. While there is difficulty in separating TSP and SO_2 effects in Philadelphia, the results are not anomalous compared to those in other cities.

Confounding by co-pollutants sometimes cannot be avoided. In studies where sensitivity analyses demonstrate that including other pollutants in the model cause little change in either the RR estimate for PM or the width of the confidence interval for the PM effect, one may conclude that the model is not seriously confounded by co-pollutants. Some studies of PM-related mortality or morbidity have shown the specific relative risk estimates for PM only in the respective models to be little changed by inclusion of other co-pollutants in the model, suggesting little confounding in those cases. On the other hand, in those analyses where the RR estimate for PM was notably diminished by inclusion of other co-pollutants in the model (indicative of some confounding), the PM effect typically still remains statistically significant, although reduced. Since a number of mortality and morbidity studies have shown that the PM effect on health is not sensitive to other pollutants, we may conclude that findings regarding the PM effects are valid.

13.4.2.5 Coherence of Epidemiologic Findings

Factors involved in evaluating both the data and the associations between exposure variables and outcome variables derived from epidemiological studies, include the strength of the association; the consistency of the association, as evidenced by its repeated observation by different investigators, in different places, circumstances and time; and the consistency of the association with other known facts (Bates, 1992). To provide a more comprehensive synthesis of available information, coherence or the logical or systematic interrelationships between

different health indices, should be evaluated. Making the case for causality in regard to observed epidemiologic associations would be further strengthened by biological plausibility, consistency or replication of findings, and coherence. The difficulty with discussing any index of internal coherence is that it requires a series of judgments on the reliability of the individual findings and observations. Thus the outcome of a coherence discussion is qualitative not quantitative. Bates (1992) also noted that the strength of the association of different health indices with exposure are important, as are difficulties in assessing exposure, and suggests three areas to look for coherence: (1) within epidemiological data, (2) between epidemiological and animal toxicological data, and (3) among epidemiological, controlled human and animal data.

Coherence considers the logical and systematic relationships among various health outcomes that may be related to exposure. For example, the biologic mechanism underlying a reversible acute pulmonary function test reduction in children is most likely not part of the acute basis for a change in the mortality rate in adults. In assessing coherence, one should compare outcomes that look at similar time frames—daily hospitalizations compared to daily mortality rather than monthly hospitalizations.

There are now available a large number of community epidemiologic studies that specifically assess health effects of ambient exposure to at least one of the following four PM indicators: (1) thoracic PM (PM_{10} or PM_{15}); (2) fine PM; (3) coarse PM; (4) sulfate and acid PM. Most of this body of indicator-specific evidence has appeared since the previous PM AQCD and promulgation of the U.S. EPA air quality standards for PM_{10}. To assist in the assessment of overall coherence across the relevant available epidemiologic database, it is helpful to summarize this evidence qualitatively.

Tables 13-6 and 13-7 present qualitative summaries of findings from community epidemiologic studies that specifically assess health effects of ambient exposure to one or more of the above four PM indicators. Table 13-6 summarizes findings on short-term exposure and table 13-7 summarizes findings on long-term PM exposure. For each PM indicator, the tables summarize findings for the health measures in the indicated population groups. The first step in preparing these tables was to develop separate layouts of cells for findings on short-term and long-term ambient PM exposures. The next step was to identify citations in the reference list of Chapter 12 that pertained to each individual cell. Community epidemiologic studies were included regardless of location and magnitude of ambient air pollution exposures. Review

articles, abstracts, and occupational studies were not included. For each table, all references used to derive the rating for each cell are presented in Appendix 13A.

Studies in which the analyzed PM exposure variable was TSP, BS, COH or some other PM surrogate were not included, unless gravimetric PM measurements had also been made in the study location which could serve as a basis for quantitative conversion to, or confident qualitative inference as to, levels of one or more of the PM indicators considered in these tables as per footnotes for each table.

Within each cell, the identified citations were qualitatively evaluated as a whole. In this evaluation, first consideration was given to the consistency of findings pertinent to a given cell. The following additional factors were also considered in this evaluation: (1) magnitude and statistical significance of observed effects estimates; (2) statistical power of study designs (dependent mainly on clarity of exposure-based comparisons, numbers of subjects, and durations of studies); and (3) pertinent information allowing reasonably confident relating of reported health effects to one or another of the specified PM indicators versus other pollutant measures.

Finally, each cell received a qualitative summary rating within the following 6-category scale: +++; ++; +; +/-; ID; and 0. This scale does not include a rating of "negative" because uniformly negative results were not observed in any cell for which pertinent studies were identified. The rating categories are described below.

Rating	Description
+++	Many studies identified and findings highly consistent across most or all studies, or fewer studies identified but findings highly reproducible and observed effects relatively large and statistically significant at $p \leq 0.05$.
++	Findings generally consistent across two or more studies and observed effects generally statistically significant, or relatively few studies identified and observed effects highly reproducible and statistically significant.
+	Findings somewhat mixed but generally consistent and at least some observed effects statistically significant, or few studies identified but incisive tests of effect were possible and results were generally statistically significant at $p \leq 0.05$.
+/-	Few pertinent studies identified, weight of evidence somewhat positive but uncertain. Usually at least one or more marginally significant ($p \leq 0.10$) PM-related effects reported.

ID	Insufficient data: at least 1 pertinent study identified but inference as to weight of evidence not warranted.
0	No pertinent studies identified.

Tables 13-6 and 13-7 may be useful in providing the reader with an overview of the more specifically-targeted available epidemiologic studies, in assessing the relative health effects of specific components of the thoracic PM complex, in assessing the relative sensitivity of different subpopulations to ambient PM exposure, and in identifying needs for future epidemiologic research.

It is emphasized that Tables 13-6 and 13-7 are intended to assist in the overall evaluation of available epidemiologic evidence, not to substitute for it. The reader is strongly cautioned not to interpret these tables beyond their appropriate limits of inference. For example, these tables are silent with respect to many other epidemiologic studies of clear, continuing relevance in the PM risk assessment and risk management process, including important recent studies for which the sole PM exposure index was TSP and most other studies in which indices for ambient PM mass were not gravimetric measurements. These studies should be considered, together with the studies identified in tables 13-6 and 13-7, in assessing both the overall coherence of epidemiologic evidence and the potential public health consequences of ambient PM exposure.

Furthermore, the cell rating criteria did not include consistency of epidemiologic findings across different PM indices or other air pollutants, health indices, or population groups, or biological coherence of epidemiologic findings with experimental findings. Thus, these tables, alone, are not intended to yield conclusions bearing on important broader issues

TABLE 13-6. QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON SHORT-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS

		Health Measure and Pollutant															
		Mortality				Hospitalization and Outpatient Visits				Community-Based Morbidity/Symptoms				Changes in Lung Function			
Population Group	Subgroup	ThP	FP[1]	CP[2]	$SO_4^=$ Acid	ThP	FP[1]	CP[2]	$SO_4^=$ Acid	ThP	FP[1]	CP[1]	$SO_4^=$ Acid	ThP	FP[1]	CP[2]	$SO_4^=$ Acid
Adults																	
	General Population	+++	++	+/-*	+	+	0	ID	0	+/-	0	0	+/-	+	0	0	0
	Elderly	+	+	0	0	++	0	0	0	0	0	0	0	0	0	0	0
	Respiratory[3]	++	+	0	0	++	+/-	ID	++	+✓	+✓	0	+✓	0	0	0	0
	Cardiovascular	+	+	0	0	+	0	0	+	0	0	0	0	0	0	0	0
Children	General Population	ID	0	0	0	+	0	ID	+/-	+	+	0	+/-	++	+	0	+
	Pre-existing Respiratory Conditions	0	0	0	0	0	0	0	0	+	+/-	0	+/-	+	ID	0	+/-
Asthmatics	Regardless of Age	0	0	0	0	++	+/-	+/-**	+	+	+/-	ID	+/-	+	+/-	ID	+/-

[1]FP = Indicator of fine-mode particles, usually $PM_{2.5}$, and ThP = Indicator of thoracic particles, typically PM_{10}.
[2]CP = Indicator of inhalable fraction of coarse-mode particles, usually (PM_{10}-$PM_{2.5}$) or (PM_{15}-$PM_{2.5}$).
[3]Respiratory causes of death.
[4]Cardiovascular causes of death.
ID = insufficient data, inference not warranted.
+/- = Few studies available, weight of evidence uncertain, but somewhat positive.
+ to +++ = Increasingly stronger, more consistent positive evidence for PM effects.
0 = No pertinent studies identified.
*Based on signficant positive association for Steubenville with CP found by Schwartz et al. (1966); but CP highly correlated with FP.
**CP not measured directly in Gordian et al. (1996) and/or Hefflin et al. (1994), but PM measured in CP-dominated polluted air.
✓ThP designation based on London BS having D_{50} cut point = 4.5 that includes some ThP particles, but probably more closely indexed FP along with acid actually measured as H_2SO_4 in Lawther et al. (1970) study.

TABLE 13-7. QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON LONG-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS

		Health Measure and PM Indicator											
		Mortality				Community-Based Morbidity/Symptoms				Changes in Lung Function			
Population Group	Subgroup	ThP	FP[1]	CP[2]	Acid-$SO_4^=$	ThP	FP[1]	CP[2]	Acid-$SO_4^=$	ThP	FP[1]	CP[2]	Acid-$SO_4^=$
Adults	General population	++	++	+/-[*]	++	+/-	+/-	0	+	+/-	0	0	ID
	Elderly	0	0	0	0	0	0	0	0	0	0	0	0
	Cardiopulmonary[3]	++	+++	0	++	0	0	0	0	0	0	0	0
Children	General population	+/-	0	0	0	+	+	0	++	+/-	ID	0	+
Asthmatic-Atopic	Regardless of Age	0	0	0	0	+	+/-	0	+/-	0	0	0	0

[1]FP = Indicator of fine-mode particles, usually $PM_{2.5}$.
[2]CP = Indicator of inhalable fraction of coarse-mode particles, usually (PM_{10}-$PM_{2.5}$) or (PM_{15}-$PM_{2.5}$).
[3]Combined cardiovascular and non-malignant respiratory causes of death.
0 = No pertinent studies identified.
ID = Insufficient data, inference not warranted.
[5]+/- = Few studies available, weight of evidence somewhat positive.
+ to +++ = Increasingly stronger, more consistent positive evidence for PM effect.
[*]Based on supplemental reanalysis by U.S. EPA of results from Dockery et al. (1993); see Figure 12-8 in Chapter 12.

such as biological plausibility of the epidemiologic findings or possible underlying mechanisms of action (which are discussed elsewhere in this chapter).

Within these important limitations, the tables suggest the following:

- Short-term exposure to ambient thoracic PM is consistently associated with adverse health effects ranging from mortality to changes in lung function. Long-term thoracic PM exposure is also strongly associated with increased mortality;
- Available evidence, though limited, suggests stronger associations of ambient fine PM exposure than coarse PM exposure with adverse health effects;
- The association of ambient PM exposure with total mortality is due primarily to its association with mortality due to respiratory and cardiovascular causes;
- There is reasonable consistency between findings on sulfate-acid exposure with findings on fine PM exposure. Because sulfates and airborne acid occur primarily in the fine PM fraction, this consistency reinforces observed associations of fine PM exposure with adverse health effects;
- Most available evidence regarding PM effects in adults comes from studies of mortality, hospitalization, and outpatient visits. Most evidence for children comes from community-based studies of morbidity, symptoms, and lung function. This impedes systematic assessment of the relative sensitivity of children and adults to ambient PM exposure;
- Very little is known about effects of long-term ambient PM exposure on chronic respiratory disease and stable lung function decrements in adults. Enhanced understanding in these areas will be especially important in assessing the biological coherence and credibility of observed associations of ambient PM exposure with increased mortality.

Table 3-8 provides further information indicative of quantitative coherence across several health endpoints, as observed in various PM epidemiology studies. The entries in the upper half of the table are for the whole population, including all age groups (designated as ALL). Overall, the data indicate that PM does have a relationship with a continuum of several health outcomes. Elevated mortality is the endpoint most clearly demonstrated to be affected in numerous studies, and represents the key endpoint for which coherence is sought in relation to other endpoints. The mortality studies suggest that mortality attributed to specific causes (respiratory,

cardiovascular) show stronger relationships (i.e., larger RR estimates) to PM measures than total mortality.

The health outcome potentially most related to cardiorespiratory mortality is hospital admissions for respiratory or cardiovascular causes in older age groups (i.e., > 65 years). In a qualitative sense, the increased mortality associated with ambient PM found in that age group should also be paralleled by increased hospital admissions within a similar time frame. Unfortunately, this issue has not been addressed specifically in relation to PM_{10} exposures by those studies yielding the above results for the population as a whole. Information from other studies directly evaluating increased mortality and morbidity risk among the elderly in related to PM_{10} measures is presented in the bottom half of Table 13-8.

A general way to assess quantitative coherence is to compare reported acute mortality and acute hospitalization risk estimates. One would expect that hospitalization would occur substantially more frequently than mortality, even though many deaths attributed to air pollution probably do not occur in hospital. Table 13-8 shows that this is indeed the case, using RR estimates developed in Chapter 12. For all age groups, expected respiratory mortality attributable to a 50 $\mu g/m^3$ increment in PM_{10} is about 0.3 deaths per day per million people (based on analyses without copollutants at sites with 3 to 5 d averaging times), whereas 2.0 daily hospital admissions per million people for respiratory conditions attributable to PM_{10} would be expected in the whole population. Similarly, 0.9 cardiovascular deaths per million per day can be projected to be associated with a 50 $\mu g/m^3$ increase in PM_{10}, compared to 2.3 hospital admissions for cardiovascular causes attributed to a comparable PM_{10} increase. For age 65+, a total of 1.0 deaths per day from all causes attributed to PM_{10} exposure might occur, whereas a larger number of daily hospital admissions would be expected for the two most common first-listed diagnoses, total respiratory conditions and heart disease. While there are some small numerical inconsistencies in Table 13-8, the coherence between the daily mortality results and the daily hospital admissions results is reassuring, considering the great diversity in study populations and analytical methods on which these estimates are based.

More specifically, we would expect 23.6 deaths per day per million people, of whom 17.0 would be age 65+ years, and 23.6 - 17.0 = 6.6 less than 65 years. Both the absolute number (17.0 per million) and the age-specific rate (17.0/126,000) are higher in the elderly.

TABLE 13-8. QUANTITATIVE COHERENCE OF ACUTE MORTALITY AND HOSPITALIZATION STUDIES

Age Group	Health Endpoint	Population Annual Baseline Per Million Total Population	Population Daily Baseline Per Million Total Population	PM_{10} Lag Time	Excess Risk per 50 $\mu g/m^3$ PM_{10} Incr.	Possible Number of PM-Related Events Per Day Per 1 Mil. Pop. for 50 $\mu g/m^3$ PM_{10} Increment
Whole Population						
All	Total mortality	8,603[1]	23.6	<2d	0.03[2]	0.7
				3-5d	0.06[2]	1.5
	Total hospit.	124,110[3]	340.0	-	-	-
All	Resp. mortality	676[1]	1.85	3-5d	0.19[4]	0.3
	Total resp. hospitalization	12,180[3]	33.4	<2d	0.06[5]	2.0
All	Cardiovascular mortality	3,635[1]	10.0	3-5d	0.09[4]	0.9
	Heart disease hospitalization	21,310[3]	58.4	<2d	0.04[6]	2.3
Elderly						
65+	Total mortality	6,201[7]	17.0	2d	0.06[8]	1.0[8]
	Total hospit.	42,845[9]	117.4	-	-	-
65+	Total resp. hospitalization	5,101[9]	14.0	≤1d	0.08[5]	1.1
	Pneumonia hospit.	2,335[9]	6.4	≤1d	0.08[10]	0.5
	COPD hospit.	2,560[11]	7.0	≤1d	0.16[5]	1.1
	Heart disease hospitalization	13,502[9]	37.0	≤1d	0.06[6]	2.2

[1]From National Center for Health Statistics (1993).
[2]From EPA meta-analyses, Table 12-30, models without copollutants.
[3]From Table 12-6, based on first-listed diagnoses for discharges.
[4]From Pope et al. (1991), Schwartz (1993) for Utah Valley and Birmingham, variance-weighted average, Table 12-4.
[5]From Table 12-8, average.
[6]From Table 12-11.
[7]Assuming elderly as 12.6% of 1991 U.S. population.
[8]Based on different set of studies than for above whole population (ALL), i.e., 65+ PM mortality risk from Saldiva et al. (1994) and Ostro et al. (1996) variance-weighted average; Section 12.3.
[9]From Table 12-6, assuming 12.6%, age 65+.
[10]From Table 12-10, average.
[11]From 1992 detailed tables; excludes asthma (ICD 493).

The excess risk estimates for the elderly subpopulation and for the population as a whole are drawn from different studies in different communities, however, and therefore one should not expect complete consistency among estimates of excess mortality shown here to be attributable to an increment of 50 $\mu g/m^3$ PM_{10}. The expected number for the whole population, using the

short averaging time, is 0.03 (23.6) = 0.7 deaths per million, compared to 0.06 (17.0) = 1.0 deaths per million in the elderly. However, the difference of -0.3 is not attributable to beneficial effects of PM_{10}, but to uncertainty in the relative risk estimates and to the superposition of results from different studies; the difference is not statistically significant. The observation that there is not a significant excess of total deaths attributable to PM_{10} beyond deaths of elderly people attributable to PM_{10} suggests that the number of deaths in younger people attributable to PM_{10} is relatively small. There have been few efforts to establish age-specific PM mortality rates, however, (Lyon et al., 1995)
with a little evidence for excess mortality in young children. Some studies for TSP suggest little excess mortality for young adults (Schwartz, 1994b; Wyzga and Lipfert, 1995) and increasing attributable excess risk with increasing age.

The element of coherence is further strengthened by those studies in which increased frequency of different health outcomes associated with PM are found in the same population. If the PM effect on mortality and hospitalization were real, we would expect to observe PM-associated mortality and hospitalization from the same conditions in the same populations. This has indeed been observed in several populations, as summarized below:

- Detroit: Mortality mainly in elderly populations, hospital admissions for respiratory causes and for cardiovascular causes in the elderly;
- Birmingham: Mortality mainly in the elderly, hospital admissions for the elderly;
- Philadelphia: Mortality and hospital admissions for pneumonia in the elderly;
- Utah Valley: Mortality and hospital admissions for respiratory causes in adults.

In the latter study, in addition to hospital admissions, other outcomes were associated with PM episodes including decrements in peak flow, increased respiratory symptoms and medication use in asthmatics, and elementary school absences. The presence of a primarily non-smoking population more or less eliminates smoking as a source of confounding. While these multiple outcomes did not occur in strictly identical subgroups of each population, there was probably a sufficient degree of overlap to indicate that PM was a significant predictor of a broad range of related health outcomes within this community. Significant decrements in pulmonary function and increased incidence of symptoms were associated with daily increases in PM in children in Utah Valley, along with a "quality of life" effect measured by lost school days. Thus, there is evidence for increased risk of health effects associated with PM exposure that range in severity

from asymptomatic pulmonary function decrements, to respiratory and cardiopulmonary illness requiring hospitalization, to excess mortality from respiratory and cardiovascular causes, especially in those older than 65 years of age.

13.5 POTENTIAL MECHANISMS AND EFFECTS OF SELECTED PM CONSTITUENTS

Epidemiologic studies have suggested that ambient particulate exposure may be associated with increased mortality and morbidity at PM concentrations below those previously thought to affect human health (Chapter 12). This section discusses the nature of observed effects reported in the above-discussed epidemiologic observational studies and attempts to interrelate such findings to available supporting information on hypothesized potential mechanisms of action that might contribute to increased human morbidity and mortality. Also discussed is information from limited controlled human and laboratory animal studies pertaining to identification of specific ambient PM constituents as possible etiologic contributors to reported ambient PM effects.

13.5.1 Characteristics of Observed Morbidity and Mortality

To approach the difficult problem of determining if the association between low-level PM concentrations and daily morbidity and mortality is biologically plausible, one must consider: the chemical and physical characteristics of the particles in the inhaled atmospheres; the characteristics of the morbidity/mortality observed and the affected population; as well as potential mechanisms that might link the two. Several salient considerations related to the evaluation of biological plausibility of the epidemiology findings are discussed below.

If daily mortality rates are associated with elevated ambient particulate concentrations, it is important to examine the specific causes of death to determine if they could plausibly be contributed to by inhaled PM. Schwartz (1994b,c) compared causes of death in Philadelphia on high pollution days (average TSP = 141 $\mu g/m^3$) with causes of deaths on lower pollution days (average TSP = 47 $\mu g/m^3$). On the high pollution days there was a higher relative increase in deaths due to: COPD (RR = 1.25); pneumonia (RR = 1.13); cardiovascular disease (RR = 1.09); and stroke (RR = 1.15). There was also a higher relative age at death and an increase in reports

that respiratory factors may have contributed to the cause of death. The causes of death and age at death were found to be similar to those observed in the London smog deaths of 1952.

Studies of associations of morbidity with particulate pollution noted small decreases (2 to 2.5%) in spirometry (FVC or FEV_1) in smokers and nonsmokers on high pollution days (60 to 100 µg/m^3; Pope and Kanner, 1993; Chestnut et al., 1991), an increased number of asthma attacks (Pönkä, 1991), and increased outpatient visits for asthma (Gordian et al., 1996) and bronchitis (but not for asthma) (Hefflin et al., 1994). Thus, the characteristics of health effects on high particle pollution days are mainly cardiopulmonary in nature and are the types of effects that can be considered plausibly related to airborne toxicants.

Data on the lung function effects of particle exposures in persons with pre-existing pulmonary disease compared to healthy persons do not yield a clear picture although they are logically likely to be more susceptible to effects from exposure to particulate pollutants. Pope and Kanner (1993) reported an approximate 2% decline in FEV_1 in smokers with mild to moderate COPD during an increased concentration in ambient PM_{10} of 100 μg/m^3 in Salt Lake City. However, in controlled exposures to similar concentrations of H_2SO_4, persons with mild COPD (average FEV_1/FVC ratio 56%) had no reduction in spirometry (Morrow et al., 1994). Exercising mild asthmatics may (Morrow et al., 1994; Koenig et al., 1989) or may not (Avol et al., 1990) experience slight bronchoconstriction following similar acid aerosol exposures. Using an elastase-induced rat model of emphysema, Mauderly et al. (1990) found that exposure to diesel exhaust, which contains aggregates of ultrafine soot particles, resulted in less particle deposition in the lungs of emphysematous rats than in normal rats, thus sparing the emphysematous rats the health effects induced by the soot particles in normal animals.

A portion of PM-related deaths may occur during short-term ambient PM episodes in persons who would have died within days or weeks. For this portion, a "harvesting effect" would logically be expected in the daily mortality statistics. That is, after the episode-related increase in mortality, the daily mortality count should decline below baseline, because some of those at risk would already have died. This decline would be expected within the period of PM-induced life shortening.

Kunst et al. (1993) have reported a harvesting effect with temperature-related mortality, and some epidemiologic studies (Cifuentes and Lave, 1996 and Spix et al., 1993) have reported such effects to be associated with episodic ambient PM exposure. Even if true PM-related

harvesting exists, epidemiologic studies may generally not be sensitive enough to detect it, because the PM effect on overall mortality is relatively small, and because it is likely that multiple mechanisms with variable time courses are involved in PM-related mortality. For example, in the 1952 London fog episode, daily mortality did not quickly return to baseline following the peak in excess deaths. Rather, mortality remained somewhat elevated in the days after pollution levels had returned to baseline (Logan, 1953). This observation suggests that among the deaths associated with short-term ambient PM exposure, the time of life lost is variable.

Particle exposure could conceivably increase susceptibility to infection with bacteria or respiratory viruses, leading to an increased incidence of respiratory infections such as pneumonia in susceptible members of the population. Potential mechanisms could include slowing of mucociliary clearance, impairment of alveolar macrophage function, and other specific or nonspecific effects on the immune response. Incubation periods for common pneumonias are in the range of 1 to 3 days although some forms require substantially longer (Benenson, 1990) and the relative risk of death from pneumonia was positively associated with ambient PM in Philadelphia. If pollutant exposure increased susceptibility to infectious disease, it might be possible to detect differences in the incidence of such diseases in communities with low versus high PM concentrations (Utell and Framptom, 1995). If so, emergency room visits and hospitalizations for pneumonia caused by the relevant agent could be measurably higher on days following elevated ambient particle concentrations. Schwartz (1994a,b) reported increased risk (RR 1.19; 95% CI, 1.07 to 1.32) for pneumonia hospitalization associated with PM_{10} (100 $\mu g/m^3$) in Birmingham for patients aged 65 and older. On the other hand, although bronchitis and asthma admissions for children were increased approximately twofold in association with operation of a steel mill in the Utah valley, pneumonia admissions for all ages were not increased. Laboratory animal data to support a direct causal link between PM exposure and death induced by pneumonia pathogens are not available. Although exposure to acidic aerosols has been linked with alterations in mucociliary clearance, non-acidic aerosols and other PM species have not been shown experimentally to cause increased susceptibility to infection in otherwise healthy young animals. Infectivity studies in old animals, as models of chronic respiratory disease, could be potentially instructive in this regard.

Particulate air pollution might also aggravate the severity of underlying chronic lung disease. This mechanism could explain increases in daily mortality and longitudinal increases in mortality if individuals with chronic airways disease experienced more frequent or severe exacerbation of their disease, or more rapid loss of function as a result of particulate exposure. If so, increased hospital admissions for specific respiratory causes should be associated with PM. There are numerous examples (cited in Chap. 12) of increased hospital admissions for COPD, bronchitis, and asthma being associated with variations in PM levels.

13.5.2 Possible Mechanisms of PM-Induced Injury

Several potential pathophysiologic mechanisms can be proposed by which low level ambient particle concentrations could conceivably contribute to morbidity and mortality. As discussed in Chapter 11, PM has been identified as causing a variety of health effects including respiratory symptoms, mechanical changes in lung function, alteration of mucociliary clearance, pulmonary inflammatory responses and morphological alterations in the lung. In addition, PM has been associated with respiratory illness, hospital admissions, and increased daily mortality.

In this section, attention is directed at pulmonary and cardiovascular mechanisms which could hypothetically contribute to increased morbidity and mortality, although it is acknowledged that specific mechanisms of action for PM are not yet well known. The phenomenon of particle related mortality may include: (1) "premature" death (or mortality displacement), that is the hastening of death for individuals already near death (i.e., hastening of certain death by hours or days); (2) increased susceptibility to infectious disease; and (3) exacerbation of chronic underlying cardiac or pulmonary disease (Utell and Frampton; 1995). The distribution of deposition of particles inhaled into the respiratory tract depends on their size, shape, chemical composition, and the airway geometry and pulmonary ventilation characteristics of the organism. The mechanisms responsible for the broad range of particle-related health affects will vary depending on the site of deposition. Once deposited, the particles may be cleared from the lung, translocated into the interstitium, sequestered in the lymph nodes, metabolized or otherwise transformed by mechanisms described in Chapter 10.

Deposition of particulate matter in the human respiratory tract could initiate events leading to increased airflow obstruction, impaired clearance, impaired host defenses, or increased epithelial permeability. Airflow obstruction could result from laryngeal constriction or

bronchoconstriction secondary to stimulation of receptors in extrathoracic or intrathoracic airways. In addition to reflex airway narrowing, reflex or local stimulation of mucus secretion could lead to mucus hypersecretion and could eventually contribute to mucus plugging in small airways. Finally, in airways disease with localized airway narrowing or obstruction, PM will tend to accumulate more rapidly.

One component of PM, namely acid aerosols, is known to cause slowing of mucociliary clearance. Since this mechanism is important in clearing particles from the lung, including biologically active particles such as spores, fungi, and bacteria, impairment of mucociliary clearance could lead to increased PM burdens, inflammation, and infection. Alveolar clearance may also be impaired through alterations in macrophage function including decreased phagocytosis, depression of mobility, and decreased adherence to surfaces. Macrophages play an important role in removing and digesting particles and may be involved in facilitating translocation of PM to either other parts of the lung or into the vascular system.

PM may transport reactive oxygen species or increase their formation. PM may induce or enhance an inflammatory response in the lung; such an effect may depend on particle size and hence deposition site as well as on chemical or biological composition of the particles. Inflammatory responses can lead to increased permeability and possibly diffusion abnormality. Retention of PM may be associated with the initiation and/or progression of COPD. In addition, mediators released during an inflammatory response could cause release of factors in the clotting cascade that may lead to an increased risk of thrombus formation in the vascular system (Seaton et al., 1995).

Pulmonary changes that contribute to cardiovascular responses include a variety of mechanisms which can lead to hypoxemia, including bronchoconstriction, apnea, impaired diffusion, and production of inflammatory mediators. Hypoxia can lead to cardiac arrhythmias and other cardiac electrophysiologic responses that in turn may lead to ventricular fibrillation and ultimately cardiac arrest. Additionally, many respiratory receptors have direct cardiovascular effects. Stimulation of C-fibers leads to bradycardia and hypertension, while stimulation of laryngeal receptors can result in hypertension, cardiac arrhythmia, bradycardia, apnea, and even cardiac arrest. Nasal receptor or pulmonary J-receptor stimulation can lead to vagally mediated bradycardia and hypertension (Widdicombe, 1988). Unfortunately, little is known about the effects of aging on airway receptor reflexes and their cardiac effects, and

limited research evaluating potential triggering of terminal cardiac events (e.g., arrhythmias) by inhaled ambient PM is only now beginning to yield preliminary results.

In addition to possible acute toxicity of particles in the respiratory tract, particles that deposit in the lung may induce inflammation. The response of the respiratory tract to such particles includes the release of numerous cytokines from alveolar macrophages and epithelial lining cells that promote healing and repair. With repeated cycles of acute lung injury and repair or with the persistence of toxic particles chronic lung injury could develop. Although such acute responses are well known, they typically occur only after several days or weeks of exposure to airborne particle concentrations many fold higher than those ambient exposures that have been shown to be associated with increased mortality and morbidity in epidemiology studies.

13.5.3 Specific PM Constituents: Acid Aerosols

Acid aerosol exposure in controlled human exposure and laboratory animal toxicology studies has been shown to cause a variety of effects on the respiratory system. In humans acutely exposed to acid aerosols, these include decrements in lung function, slowing of mucociliary clearance, and increased airway responsiveness and respiratory symptoms.

Human experimental studies indicate that healthy subjects experience only very modest decrements in respiratory mechanics following single exposures to H_2SO_4 at levels up to 2,000 $\mu g/m^3$ for 1 h. Acid aerosol deposition and neutralization models suggest that with the ammonia present in the mouth and respiratory tract of humans, a large portion of inhaled acids will be neutralized during inhalation. Nevertheless, even with exercise to decrease the time for neutralization and the use of acidic gargles to minimize the levels of oral ammonia available for neutralization, lung function and symptom responses are not appreciably enhanced in healthy subjects. Mild lower respiratory symptoms occur at exposure concentrations in the >1,000 $\mu g/m^3$ range, particularly with larger particle sizes. These observations are consistent with deposition models that indicate greater deposition of larger aerosols in the tracheobronchial region, the origin of many of the respiratory symptoms such as cough and irritation. However, these observations do not provide an explanation for the observed lower levels of FVC and FEV_1 seen in children who reside in communities with high levels of acidic PM. The only studies of controlled acid exposures in non-adults are those of adolescent asthmatics, discussed below.

Both acute and chronic exposure to H_2SO_4 can produce functional changes in the respiratory tract, some of which have a greater pathological significance than others. Acute exposure will alter pulmonary function, largely due to bronchoconstriction. However, attempts to produce changes in airway resistance in healthy animals at levels below 1,000 $\mu g/m^3$ have been largely unsuccessful. With the exception of guinea pigs, these findings in laboratory animals are similar to those for healthy humans. The lowest effective level of H_2SO_4 producing a small transient change in airway resistance in the guinea pig is 100 $\mu g/m^3$ (1-h exposure). In general, the smaller size droplets were more effective in altering pulmonary function, especially at low concentrations. Deposition models predict that only smaller aerosols (< 2-4 μm) would have appreciable tracheobronchial and alveolar deposition in small laboratory animals. Chronic exposure to H_2SO_4 is also associated with alterations in pulmonary function (e.g., changes in the distribution of ventilation and in respiratory rate in monkeys). However, in these cases the effective concentrations are ≥ 500 $\mu g/m^3$. Hyperresponsive airways have been induced with repeated exposures to 250 $\mu g/m^3$ H_2SO_4 in rabbits. Acute exposures to higher concentrations did not affect responsiveness in healthy humans but exposures in the 500 to 1,000 $\mu g/m^3$ range in asthmatics can result in changes in airway responsiveness. Because droplet aerosols are highly soluble, it is unlikely that any appreciable lung burden of these particles would accumulate.

Asthmatic subjects appear to be more sensitive than healthy subjects to the effects of acid aerosols on lung function, but the effective concentration differs widely among studies. Adolescent asthmatics may be more sensitive than adults, and may experience small decrements in lung function in response to H_2SO_4 at exposure levels only slightly above peak ambient levels. Mild bronchoconstriction has been reported after brief exposures to as low as 68 $\mu g/m^3$ H_2SO_4 in exercising adolescent asthmatics and 90 $\mu g/m^3$ in exercising adult asthmatics (Morrow et al., 1994; Koenig et al., 1989), although this has not always been observed (Avol, et al., 1990). These observations may be consistent with the association of pulmonary function decrements with acidic PM exposure in children attending summer camps. Acid aerosol probably acts as an irritant in the tracheobronchial region and increased responsiveness in this region is the likely cause of increased response of asthmatics to acids. If chronic acid exposure were to exacerbate asthma in children, this could partially account for the reduced lung function levels found in communities with higher levels of acidic PM. In very limited studies, the elderly and people

with COPD do not appear to be unusually susceptible to the effects of acid aerosols on lung function.

Acid aerosols typically cause slowing of mucociliary clearance in healthy subjects, although the effects are dependent on exposure concentration and exposure duration and on the region of the lung being studied (brief exposure to low concentrations of acid may accelerate clearance of particles deposited primarily in the tracheobronchial region). The bronchial mucociliary clearance system in laboratory animals is also very sensitive to inhaled acids. The lowest level shown to have an effect on mucociliary transport rates in healthy laboratory animals (100 $\mu g/m^3$ with repeated exposures) is well below that which results in other physiological changes in most laboratory animals and is consistent with the findings in humans exposed to acid aerosols.

The lungs have an array of defense mechanisms to detoxify and physically remove inhaled material, and available evidence indicates that certain of these defenses may be altered by exposure to H_2SO_4 levels <1,000 $\mu g/m^3$. Defenses such as resistance to bacterial infection may be altered even by acute exposure to concentrations of H_2SO_4 around 1,000 $\mu g/m^3$. Limited data also suggest that exposure to acid aerosols may affect the functioning of alveolar macrophages at levels as low as 500 $\mu g/m^3$ H_2SO_4. However, in humans, exposure to acid aerosol (1,000 $\mu g/m^3$) did not appear to induce an inflammatory response or to cause any changes in macrophage function (Frampton et al., 1992). Alveolar region particle clearance is affected by repeated H_2SO_4 exposures to as low as 125 $\mu g/m^3$, although these are still higher than currently observed ambient acid U.S. concentrations. One would expect effects from impaired pulmonary defense mechanisms to develop over an extended period of continuing exposure. Impairment of pulmonary host defense mechanisms by acidic particles is consistent with the observations of increased prevalence of bronchitis in communities with higher levels of acidic PM.

The assessment of the toxicology of acid aerosols requires some examination of potential interactions with other air pollutants. Such interactions may be antagonistic, additive, or synergistic. Evidence for interactive effects may depend upon the sequence of exposure as well as on the endpoint examined. Low levels of H_2SO_4 (40 to 100 $\mu g/m^3$) have been shown to react synergistically with O_3 in simultaneous exposures using biochemical endpoints. In this case, the H_2SO_4 enhanced the damage due to the O_3. Two recent studies have examined the effects of exposure to both H_2SO_4 and ozone on lung function in healthy and asthmatic subjects. In

contrast with several previous studies conducted at higher acid concentrations, both studies suggested that 100 $\mu g/m^3$ H_2SO_4 may cause slight potentiation of the pulmonary function response to ozone.

The surface of a particle is primarily in contact with respiratory cells and surfaces and thus any coating on a solid particle, such as acid, would be presented to the respiratory surfaces. Acid coating of ultrafine zinc oxide particles appears to enhance the effects of acid in the guinea pig, for both permeability, inflammation, and some functional responses such as changes in diffusing capacity (Chen et al., 1992; 1995). However, acid coating of fine (<1 μm) carbon particles did not enhance the responses of humans to acid aerosols (Anderson et al., 1992). The process of acid coating used by Anderson et al. (1992) is different form that used by Chen et al. (1995) and these data may not be comparable. It is unclear whether these differences can be attributed to the acid coating alone since the carrier particle (ZnO versus C) may play a role and, in the case of the ultrafine coated particles, the total number of particles *per se* may play a role in the response. Moreover, Chen et al. (1995) noted changes in intracellular pH of macrophages, which may affect phagocytosis, following exposure to aerosols of H_2SO_4 layered on carbon particles. This effect was dependant both upon the number of particles as well as the total mass concentration of H^+ in the exposure atmosphere; a threshold existed for both exposure parameters. Similar amounts of (larger) droplet acid aerosol did not produce these responses in guinea pigs. This latter

finding is consistent with a single human study of very fine acid/sulfate particle exposure in which no spirometry responses were observed at levels in excess of 1000 µg/m^3 (Horvath et al., 1987).

Human exposure studies of particles other than acid aerosols provide insufficient data to draw conclusions regarding health effects. However, available data suggest that inhalation of inert particles in the respirable range, including three studies of carbon particles, have little or no effect on symptoms or lung function in healthy subjects. Although, coating of micron-sized carbon particles with sulfuric acid did not increase pulmonary function responses, carbon particles impregnated with formaldehyde did increase the delivery of formaldehyde and consequently increased irritant responses in human subjects.

13.5.4 Specific PM Constituents: Ultrafine Aerosols

Ultrafine aerosols (<0.1 μm) are a class of particles that have the potential to cause toxic injury to the respiratory tract as seen in studies conducted both in vivo and in vitro. At high concentrations, ultrafine particles, as a metal or polymer "fume", are associated with toxic respiratory responses both in humans and in laboratory animals. Occupational exposures to high levels of polymer fumes (>1,000 μg/m^3; size <1 μm) can lead to fever, diffusion impairment, and respiratory symptoms (Dahlqvist et al., 1992; Goldstein et al., 1987). Such exposures are associated with cough, dyspnea, pulmonary edema, and acute inflammation.

Ultrafine (11 nm) particles of copper oxide inhaled at 10^9 particles/cm^3 for 60 minutes in hamsters were dispersed throughout the lung including the interstitium, the alveolar capillaries and the pulmonary lymphatics (Stearns et al., 1994). During the exposure pulmonary resistance increased four-fold and the increase persisted for 24 h. These results indicate that ultrafine particles of low solubility can rapidly breach epithelial cell barriers and penetrate to interstitial and endothelial sites.

The potential for toxicity of ultrafine particles has been studied using a polymer ultrafine particle as a model (Oberdörster et al., 1995a,b; Warheit et al., 1990). These studies indicate that freshly generated insoluble ultrafine particles, when inhaled as single particles in low concentrations (<50 μg/m^3) can cause severe injury to the lung. In addition there are studies on a number of relatively insoluble ultrafine particles (diesel, carbon black) that are present in the ambient atmosphere as aggregated ultrafines. These studies, reviewed in Chapter 11, indicate

that inhalation exposures of laboratory animals to aggregated particles, including TiO_2, carbon black particles and diesel soot are associated with epithelial cell proliferation, occlusion of interalveolar pores (of Kohn), impairment of alveolar macrophages, chronic pulmonary inflammation, pulmonary fibrosis, and induction of lung tumors. No acute effects were observed, however, even at the highest exposure concentrations.

As reviewed in Chapter 11, mechanisms which could enhance the toxicity of ultrafine particles include: the high pulmonary deposition efficiencies of inhaled singlet ultrafine particles; the large numbers of these particles per unit mass; their increased surface area available for reaction; their rapid penetration of epithelial layers and access to pulmonary interstitial sites; and the presence of radicals and perhaps acids on the particle surface. When inhaled at the same mass concentration, ultrafine particles with a diameter of 20 nm have a number concentration that is approximately 6 orders of magnitude higher than for a 2.5 µm particle; the collective particle surface area is also greatly increased (Table 11-1) Ultrafine particles present a problem to the respiratory tract because of their large collective surface area and because they can evade macrophage phagocytosis and penetrate into the interstitium more easily than larger sized particles (Takenaka et al., 1986; Ferin et al., 1990). There is evidence that some aggregated insoluble ultrafine particles may dissociate into singlet ultrafine particles in the lung (Takenaka et al., 1986; Ferin et al., 1990; Oberdorster, et al., 1994) which would facilitate transport across the epithelium. Even though the deposition of aggregated ultrafines would be similar to particles in the fine range, their behavior in the lung would be that of singlet ultrafine particles.

The occurrence of ultrafine particles as well as their sources are reviewed in Chapters 3 and 6. Single ultrafine particles occur regularly in the urban atmosphere at high number concentrations (5×10^4 - 3×10^5 particles/cm^3) but very low mass concentrations (Brand et al., 1991; 1992; Castellani, 1993). Particle number concentrations may vary from less than 1000/cm^3 at clean, background sites to over 100,000 cm^3 in polluted urban areas. Geometric mean diameter ranged from 12 to 43 nm in Long Beach, CA and 47 to 75 nm in clean air in the Rocky Mountains. Although ultrafine particles are not stable because they quickly aggregate to form larger particles, they continue to be freshly generated from a number of anthropogenic sources (e.g., gas to particle conversion; combustion processes; incinerator emissions). Moreover, the presence of ultrafine particles in human alveolar macrophages indicates

widespread exposures to ultrafines, either as singlet particles or aggregates in ambient air (Hatch et al., 1994).

At present there are no studies with ambient ultrafine particles. An important aspect of the potential toxicity of ultrafine particles is their low solubility whether they are present in the exposure atmosphere as singlet particles or as aggregates. At this point the limited data base does not permit a judgment to be made on the potential for ultrafine particles to contribute to morbidity and/or mortality consistent with the epidemiologic findings for ambient particle exposures.

13.5.5 Specific PM Constituents: Crystalline Silica

The limited data on air concentrations of silica in the United States indicate that silica particles arising from natural, industrial, and farming activities can result in estimated ambient annual average and high ambient quartz levels of 3 and 8 $\mu g/m^3$, respectively. However, silica is one of the most common substances to which workers are exposed and several extensive occupational studies clearly define the exposure levels and resultant health effects. Consequently, a causal relationship between inhalation of dust containing crystalline silica and pulmonary inflammation and the consequent development of fibrosis (silicosis) is well-established. Although a correlation between silicosis and increased risk of neoplasia is suggested by the results of recent occupational studies, experimental evidence that quartz can cause lung cancer without silicosis, has only been seen in rats. Rats appear to be more sensitive to the development of silica-induced lung injury and lung tumors than other rodent species such as mice and hamsters. Although the pulmonary pathological effects of inhaled crystalline silica are well-established, there is little information on the effects of inhaled amorphous silica. The limited information suggests that, in the absence of continuing exposures, the respiratory tract effects following exposures to amorphous silicates are reversible, and occur only in laboratory animals exposed to silica in excess of 10,000 $\mu g/m^3$ for periods ranging from days to years. The results demonstrate that the crystalline forms of silica dust were substantially more potent in producing pulmonary toxicity compared to the amorphous or colloidal forms of silica. Differences in sensitivity to inhaled silica are apparent not only across and within rodent species, but also between rodents and humans; this limits the utility of laboratory animal data for extrapolation of silica risk to ambient level exposures.

The effects of crystalline silica exposure (CSE) have been extensively studied in mining environments, and there are some clear differences between the mining environments and the ambient environment. These differences generally suggest that silica in the ambient environment is less toxic, primarily because of the larger particle sizes associated with ambient sources, the reduced likelihood of exposure to more potent "freshly fractured" silica, and less frequent peak exposures. In any case, a thorough analysis of the most extensive occupational studies available, each of which examined the medical histories of thousands of miners, suggests that the cumulative risk of silicosis among South Dakotan, Canadian, and South African miners from exposures at or below 1000 μg crystalline silica/m^3 · years is very nearly 0%. Using a high estimate of 10% for the crystalline silica fraction in PM_{10} from U.S. metropolitan areas, 1000 μg crystalline silica/m^3 · years is the highest CSE expected from continuous lifetime exposure at or below the annual PM_{10} NAAQS of 50 μg/m^3. Thus, current data suggest that, for healthy individuals not compromised by other respiratory ailments and for ambient environments expected to contain 10% or less crystalline silica fraction in PM_{10}, maintenance of the 50 μg/m^3 annual NAAQS for PM_{10} would be adequate to protect against silicotic effects from ambient crystalline silica exposures.

13.5.6 Specific PM Constituents: Bioaerosols

Ambient bioaerosols include fungal spores, pollen, bacteria, viruses, endotoxin, and animal and plant debris. Bacteria, viruses and endotoxin are mainly found attached to aerosol particles, while entities in the other categories are found as separate particles. Data for characterizing ambient concentrations and size distributions of bioaerosols are sparse. Matthias-Maser and Jaenicke (1994) found that bioaerosols constituted about 30% of the total number of particles in samples collected on a clean day in Mainz, Germany. The proportion of particles that were bioaerosols was higher in the fine size mode (as much as a third) and slightly lower in the coarse size mode. In Brisbane, Australia, Glikson et al. (1995) found that fungal spores dominate the bioaerosol count in the coarse fraction of PM_{10} and that the overall contribution of bioaerosols to total PM_{10} particulate mass was on the order of 5 to 10%. However, the cytoplasmic content of spores and pollen was often found to be adhered to particles emitted by motor vehicles and particles of crustal origin.

Fungal spores range in size from 1.5 µm to >100 µm, although most are 2 to 4 µm MMAD. They form the largest and most consistently present component of biological aerosols in ambient air. Levels vary seasonally, usually being lowest when snow is on the ground. Fungal spores often reach levels of 1000 to 10,000 spores/m^3 during the summer months (Lacey and Dutkiewicz, 1994; Madelin, 1994) and may be as high as 100,000/m^3 near some anthropogenic sources (agriculture activities, compost, etc.).

Bioaerosols can contribute to increased mortality and morbidity. Asthma mortality has been associated with ambient levels of fungal spores, unadjusted OR of 2.16 (95% CI = 1.31 to 3.56) per increment of 1000 spores/m^3; controlling for time and pollen counts reduced the RR to 1.2 (95% CI = 1.07 to 1.34) (Targonski et al., 1995). Asthma mortality in Scotland shows a seasonal peak that follows the peak in ambient pollen levels (Mackay et al., 1992). Exposure to fungal spores has also been identified as a possible precipitating factor in respiratory arrest in asthmatics (O'Hollaren et al., 1991).

Exposure to fungal spores in healthy individuals can lead to allergic alveolitis (hypersensitivity pneumonitis) or pulmonary mycoses such as coccidioidomycosis or histoplasmosis (Lacey and Dutkiewicz, 1994). Induction of hypersensitivity generally requires exposure to concentrations that are substantially higher than in ambient air, although subsequent antigenic responses require much lower concentrations. Association of fungal and pollen spores with exacerbations of asthma or allergic rhinits is well established (Ayres, 1986). The incidence of many other diseases (e.g., coccidioidomycosis) induced by fungal spores is relatively low, although there is no doubt about the causal organisms (Lacey and Dutkiewicz, 1994). The potential for fungal induced diseases is much higher in immunocompromised patients and those with unusually high exposures to crustal dust in the breathing zone, such as military personnel.

In addition to fungal spores and pollen, other bioaerosol material can exacerbate asthma and can also induce responses in nonasthmatics. For example, in grain workers who experience symptoms, spirometry decrements, and airway hyperresponsiveness in response to breathing grain dust, the severity of responses is associated with levels of endotoxin in the bioaerosol rather than the total dust concentration (Schwartz et al., 1995). A classic series of studies (Antó and Sunyer, 1990) proved that airborne dust from soybean husks was responsible for asthma epidemics and increased emergency room visits in Barcelona, Spain. These studies indicate that airborne fragments of biological substances can produce severe health effects.

Bacterial aerosol counts may range as high as 30,000 bacteria/m^3 downwind of sewage treatment facilities, composting areas, waterfalls from polluted rivers, or certain agricultural activities. Typical levels in urban areas range from several hundred to several thousand bacteria/m^3 (Lighthart and Mohr, 1994). Human pathogenic activity of such bacteria is not well understood or characterized. Infective potential of aerosolized bacteria depends on size (smaller are more effective), virulence, host immune status, and host species sensitivity (Salem and Gardner, 1994). Aerosolized bacteria can cause bacterial infections of the lung including tuberculosis and legionnaire's disease. The *Legionella pneumophila* bacterium is one of the few infectious agents known to reside outside an infected host and is commonly found in water, including lakes and streams. Levels of bioaerosols (fungi and bacteria) are generally higher in urban than in rural areas (Lighthart and Stetzenbach, 1994).

Exposures to bioaerosols of the above types, are clearly capable of producing serious health effects especially at high concentrations encountered in indoor environments.

Because of the extremely limited knowledge of ambient levels of bioaerosols and their composition and relative potency of various components, the small number of well conducted epidemiologic studies of bioaerosols, and the absence of controlled studies of ambient bioaerosols, the relative contribution of bioaerosols to the observed PM-associated morbidity and mortality effects cannot be determined with any confidence at the present time. However, it seems unlikely that bioaerosols play more than a minor role in such effects. This conclusion is based on

1. The seasonal variability in concentration of some bioaerosols whose general trends are different from the seasonal trends in mortality.
2. The subpopulation most afflicted by bioaersols is asthmatics who are not identified as a sensitive subgroup for PM-associated mortality.
3. Many of the specific diseases induced by bioaerosols have an extremely low incidence and, for many, the mortality rate is also very low.

13.6 INDIVIDUAL RISK FACTORS AND POTENTIALLY SUSCEPTIBLE SUBPOPULATIONS

In addition to risk associated with activity, location, and dosimetry, inherent individual characteristics may also affect risk from inhaled PM. For example, elderly individuals or persons with pre-existing cardiovascular or respiratory disease, particularly chronic obstructive pulmonary disease (COPD), are likely to be at greater risk from PM exposure. Both the incidence of and the death rates from cardiovascular and pulmonary diseases increase with age. The following section discusses individual risk factors, including: age, asthma, COPD, and cardiovascular disease. The incidence of selected cardiopulmonary diseases by age and geographic region is presented in Table 13-9 to help place the following discussion in perspective.

13.6.1 Age

Certain population groups such as the elderly may be more sensitive to changes in pulmonary or cardiovascular function because of age-related decrements in physiological reserve. For example, cardiorespiratory function, including lung volumes, FEV_1, maximum oxygen uptake, and cardiac output reserve decline with age (Folkow and Svanborg, 1993; Dice, 1993; Lakatta, 1993; Kenney, 1989), even in a healthy active population. Morphological changes in the lung lead to loss of lung elasticity, increased stiffness of the chest wall, enlargement of alveolar ducts and loss of alveolar septa including diminished numbers of pulmonary capillaries, and increased numbers of mucous glands. Many of the decrements in physiological function associated with the aging process also may be associated with pathological changes caused by disease or other environmental stressors impacting a person over their lifespan.

If the pulmonary clearance mechanisms are impaired due to pulmonary disease, aging, or repeated inhalation exposures that are toxic to the normal clearance mechanisms, then particles and their metabolic or degradation products may persist. The degree to which an added particle burden may impact an individual will likely be affected by their age, health status, medication usage and their overall susceptibility to this inhalation exposure. One factor that may promote increased risk in the older population is that, over their lifespan,

TABLE 13-9. INCIDENCE OF SELECTED CARDIORESPIRATORY DISORDERS BY AGE AND BY GEOGRAPHIC REGION (reported as incidence per thousand population and as number of cases in thousands)

		Age				Regional			
Chronic Condition/Disease	All Ages	Under 45	45-64	Over 65	Over 75	NE	MW	S	W
COPD									
Incidence/1,000 persons	61	50	63	104	107	56	63	63	61
No. cases × 1,000	15,400	8,650	3,550	3,210	1,200				
Asthma									
Incidence/1,000 persons	49	52	45	40	34	48	49	48	52
No. cases × 1,000	12,370	9,000	2,180	1,230	420				
Heart Disease									
Incidence/1,000 persons	86	29	135	325	404	89	84	93	74
No. cases × 1,000	21,600	5,050	6,540	10,000	4,980				
HD-ischemic									
Incidence/1,000 persons	32	3	61	153	184	37	29	37	24
No. cases × 1,000	8,160	490	2,970	4,702	2,270				
HD-rhythmic									
Incidence/1,000 persons	33	20	44	83	104	33	35	32	31
No. cases × 1,000	8,160	3,500	970	2,550	1,275				
Hypertension									
Incidence/1,000 persons	111	34	226	358	352	106	115	123	91
No. cases × 1,000	27,820	5,830	10,980	11,000	4,300				

Source: National Center for Health Statistics (1994).

they have had more exposure and hence more opportunity to accumulate particles or damage in their lungs.

Cardiorespiratory system function may be compromised and become less efficient in older people and as a result of disease. For example in people over 75 years, 40% have some form of heart disease and 35% have hypertension. Approximately 10% of the population in this age group has COPD. (See table 13-9) Responses to particle inhalation could, conceivably, further compromise the functional status in such individuals. The terminal event(s) of life must presumably result from a triggering or exacerbating of a lethal failing of a critical function, such as ventilation, gas exchange, pulmonary circulation, lung fluid balance, or cardiovascular function in subjects already approaching the limits of tolerance due to preexisting conditions.

13.6.2 COPD

The conditions most likely to be affected by inhaled PM are the chronic airways diseases, particularly COPD. COPD is the fourth leading cause of death in the United States, and is the most common cause of non-malignant respiratory deaths, accounting for more than 100,000 deaths in 1993 (National Center for Health Statistics, 1996). According to the International Classification of Disease (ICD) definitions and classification codes, asthma is included along with emphysema, chronic bronchitis, and pnuemonitis under the classification of COPD (490-496). In discussions of epidemiological studies that included this range of ICD codes, asthma is included under COPD unless Code 493 is specifically excluded. In the discussion in Chapters 11 and 13, we have included only emphysema and chronic bronchitis in accord with the view espoused in a recent official statement of the American Thoracic Society (1995).

This group of diseases encompasses emphysema and chronic bronchitis, but information on death certificates may not allow differentiation between these diagnoses. The pathophysiology includes chronic inflammation of the distal airways as well as destruction of the lung parenchyma. Loss of supportive elastic tissue leads to airway closure during expiration, resulting in obstruction of flow. Processes that enhance airway inflammation or edema lead to constriction of the conducting airways or slowing of mucociliary clearance that could adversely affect gas exchange and host defense. Moreover, the uneven matching of ventilation and perfusion characteristic of this disease, with dependence on fewer functioning airways and

alveoli for gas exchange, means inhaled particles may be directed to the remaining functional lung units in higher concentration than in healthy lungs (Bates, 1992)

In comparison to healthy people, individuals with chronic respiratory disease have greater deposition of inhaled aerosols that would be contained in the fine ($PM_{2.5}$) mode (see Chapter 10). The deposition of particles in the lungs of a COPD patient may be as much as three-fold greater than in a healthy adult. Thus, the potential for greater target tissue dose in susceptible patients is present. The lungs of individuals with chronic lung diseases, such as asthma, bronchitis, or emphysema are often in a chronic state of inflammation. In addition to the fact that particles can induce an inflammatory response in the respiratory region, the influence of particles on generation of proinflammatory cytokines is enhanced by the prior existence of inflammation. Phagocytosis by alveolar macrophages is down-regulated both by inflammation and the increased volumes of ingested particles. Therefore, people with lung disease not only have greater particle deposition, but the conditions that exist in their lungs prior to exposure are conducive to amplification of the effects of particles and depression of their clearance.

Particles, especially submicron particles, could also act at the level of the pulmonary vasculature by eliciting changes in pulmonary vascular resistance that could exacerbate ventilation perfusion abnormalities in people with COPD. Emphysema destroys alveolar walls and pulmonary capillaries causing a progressive increase in pulmonary vascular resistance, pulmonary blood pressure, and interstitial edema, eventually leading to systemic hypoxia. This results in an increased workload on the heart and increases the risk of heart failure.

Patients admitted to an intensive care unit for acute COPD exacerbations have a substantial hospital mortality (possibly as high as 25%) rising to an overall mortality that may approach 60% within one year of the admission. For patients 65 years and older, the mortality is substantially higher than for younger patients (Seneff et al., 1995). Mortality is often associated with non-respiratory system organ dysfunction and thus causes of death may be misclassified.

13.6.3 Cardiovascular Disease

Particulate pollutants have been associated with increases in cardiovascular mortality both in the historic major air pollution episodes and in the more recent time-series analysis. Approximately eight times as many deaths are caused by heart disease as by chronic respiratory disease. Bates (1992) has postulated three ways in which pollutants could affect cardiovascular mortality statistics. These include: acute airways disease misdiagnosed as pulmonary edema; increased lung permeability, leading to pulmonary edema in people with underlying heart disease and increased left atrial pressure; and acute bronchiolitis or pneumonia induced by air pollutants precipitating congestive heart failure in those with pre-existing heart disease. Moreover, the pathophysiology of many lung diseases is closely intertwined with cardiac function. Many individuals with COPD also have cardiovascular disease caused by: smoking, aging, or pulmonary hypertension accompanying COPD. Terminal events in patients with end-stage COPD are often cardiac, and may therefore be misclassified as cardiovascular deaths. Furthermore, hypoxemia associated with abnormal gas exchange can precipitate cardiac arrhythmias and lead to sudden death.

13.6.4 Asthma

Asthma is a common chronic obstructive respiratory disease that may be exacerbated by air pollution. Asthmatics are known to be more sensitive to certain gaseous pollutants such as sulfur dioxide and ozone. General trends in asthma mortality (increasing) have not paralleled changes in air pollution (decreasing) (Lang and Polansky, 1994). Atmospheric particle levels have been linked with increased hospital admissions for asthma, worsening of symptoms, decrements in lung function, and increased medication use. Asthma-related mortality is relatively uncommon, accounting for approximately 5000 deaths annually or about 5% of total chronic respiratory deaths in 1991. Asthma accounts for only a small percentage of overall respiratory death in older adults. Although PM-related mortality may have a component related to asthma, the observed mortality increases cannot be accounted for by increased deaths due to asthma alone.

13.6.5 Estimating Public Health Impacts of Ambient PM Exposures in the United States

Efforts to quantify the number of deaths attributable to, and the years of life lost to, ambient PM exposure are currently subject to much uncertainty. Determination of the number of deaths attributable to a risk factor requires knowledge of the following entities: (1) the number of deaths in the population; (2) variations in the extent of exposure of the population to the factor; and (3) the relative risk of mortality that exposure to the factor confers; and (4) the shape of the underlying exposure-response relationship.

In the case of PM exposure, uncertainty arises primarily with regard to the second, third, and fourth entities. While available monitoring information provides rough estimates of likely exposures of the general population or susceptible subpopulations for PM_{10} in a number of U.S. urban locations, much less extensive information exists with regard to ambient measures of $PM_{2.5}$ or other indicators of fine particles or specific PM constituents.

As for the third entity, several sources of uncertainty would affect derivation of and application of population relative risk estimates for PM and mortality. First, risk ratios from various short-term mortality studies, while generally falling within a range of 1.02 to 1.10 (i.e., 2 to 10% increase in risk of death over background risk), do vary somewhat from site to site. Hence, it is probably most credible to use site-specific relative risk estimates in projecting numbers of PM-related health events for any particular U.S. city, rather than broad application of a single "best estimate" relative risk value across various locations. Lastly, the proportions of total PM-mediated mortality attributable to short-term and long-term PM exposure are not known, and the overlap between short-term and long-term mortality studies, that is the proportion of all PM-mediated mortality detected in both types of studies, is not known. Therefore, it would be difficult to achieve appropriate weighting of the widely-divergent short-term and long-term mortality risk ratios in projecting potential PM public health impacts.

The interpretation of the underlying exposure-response relationships is probably the most problematic issue for risk assessment purposes at this time. In the absence of clear toxicologic evidence regarding possible mechanisms of action that would plausibly explain the observed epidemiologic associations between mortality or morbidity and low-level ambient PM concentrations, one is left with a dilemma of how to interpret the underlying exposure-response relationship based only on the available epidemiologic findings.

As shown in Figure 13-5, several alternative interpretations of reported relative risk findings are reasonable with regard to possible underlying PM exposure (concentration)-health effects relationships. Most published studies report results (RR estimates) based on linear models (as illustrated by Line A in the figure), implying a possible linear, no-threshold underlying relationship that may extend to essentially zero PM concentrations (line B). However, the existing PM epidemiology data do not allow one to rule out the possible existence of an underlying non-linear relationship (e.g., the "threshold" function illustrated by Line C). The choice of one or another interpretation for risk assessment purposes has important ultimate implications. Choice of a linear, no-threshold function implied by Line B may overestimate numbers of health events (e.g., numbers of PM-related deaths or hospital visits per day or year), given the absence of evidence substantiating increased risk below the lowest observed PM concentrations used in generating the risk estimates. On the other hand, far fewer health events would be estimated for the lowest PM concentrations before any "threshold" breakpoint if the relationship implied by Curve C is assumed. Another intermediate possibility would be to assume a linear relationship down to an estimated PM "background level", as a means of projecting the number of health events that would be associated with theoretically controllable PM concentrations above "background" levels.

Unfortunately, only very limited information now exists from published analyses that might aid in resolving this interpretational dilemma. As noted earlier, most of the PM epidemiology studies report only the results of fitting a linear model for PM for the relative risk of a health effect for a specific PM increment. Only a few studies provide additional information by which to assess the adequacy of the linear model assumption. Nonlinear smoothing splines have been shown by Schwartz (1994b) and by Samet et al. (1995) for their Philadelphia mortality studies, by Schwartz (1994a) for the Cincinnati mortality study, by Schwartz (1993) for the Birmingham PM_{10} mortality study, and by Schwartz for a number of hospital admissions studies. Linear splines were shown by Cifuentes and Lave (1996) for a different set of Philadelphia TSP mortality data. The TSP mortality curves shown in Chapter 12 are compared in Figure 13-6, along with linear models based in part on the same studies. Both the TSP models fitted without copollutants (Cincinnati, Philadelphia 1973 to 1980) and

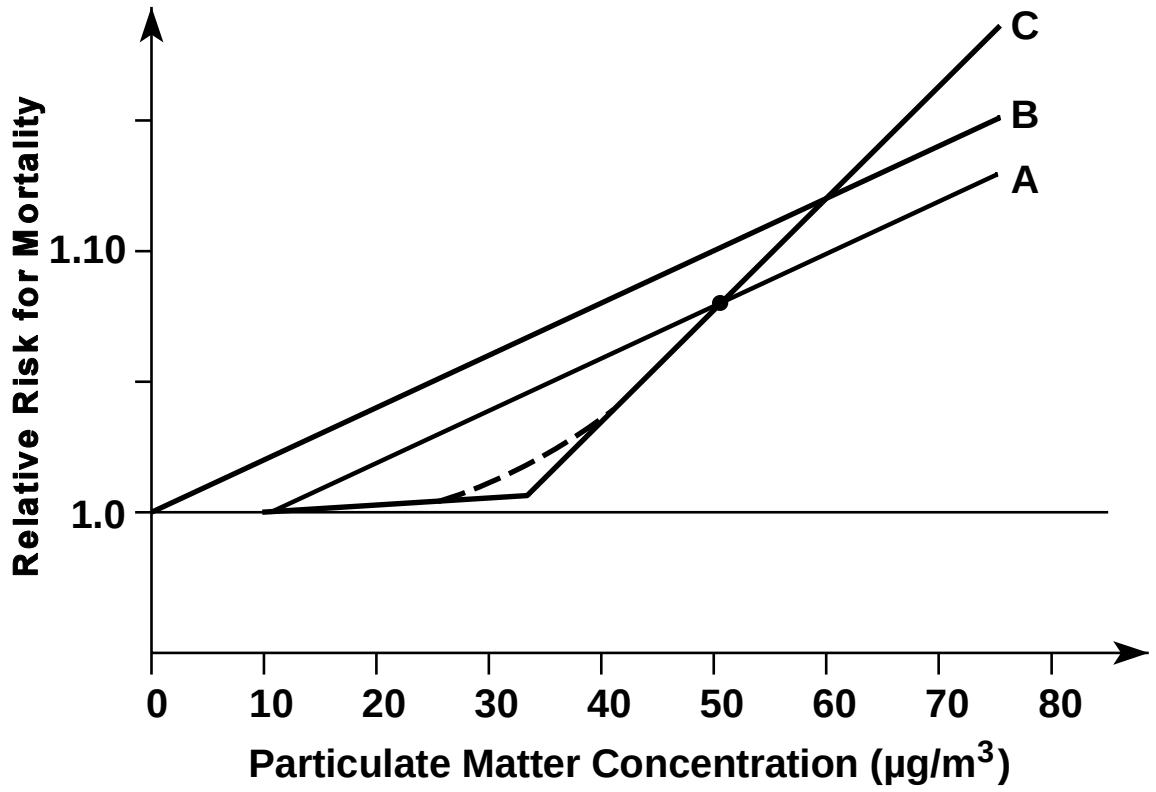

Figure 13-5. Schematic representation of alternative interpretations of reported epidemiologic relative risk (RR) findings with regard to possible underlying PM mortality concentration-response functions. Published studies typically only report results from linear models that estimate RR over a range of observed PM concentrations as represented by Line A (specific PM values shown are for illustrative purposes only), compared against baseline risk (RR = 1.0) at the lowest observed PM level. One alternative interpretation is that the RR actually represents an underlying linear, no-threshold PM-mortality relationship (Line B) with the same slope as Line A but extending below the lowest observed PM level essentially to 0 μg/m^3. Another possibility is that the underlying functional relationship may have a threshold (illustrated by Curve C), with an initially relatively flat segment, not statistically distinguishable from the baseline risk (1.0) until some PM concentration where it sharply increases (or more likely somewhat less sharply ascends in the vicinity of the breakpoint as shown by the dashed lines).

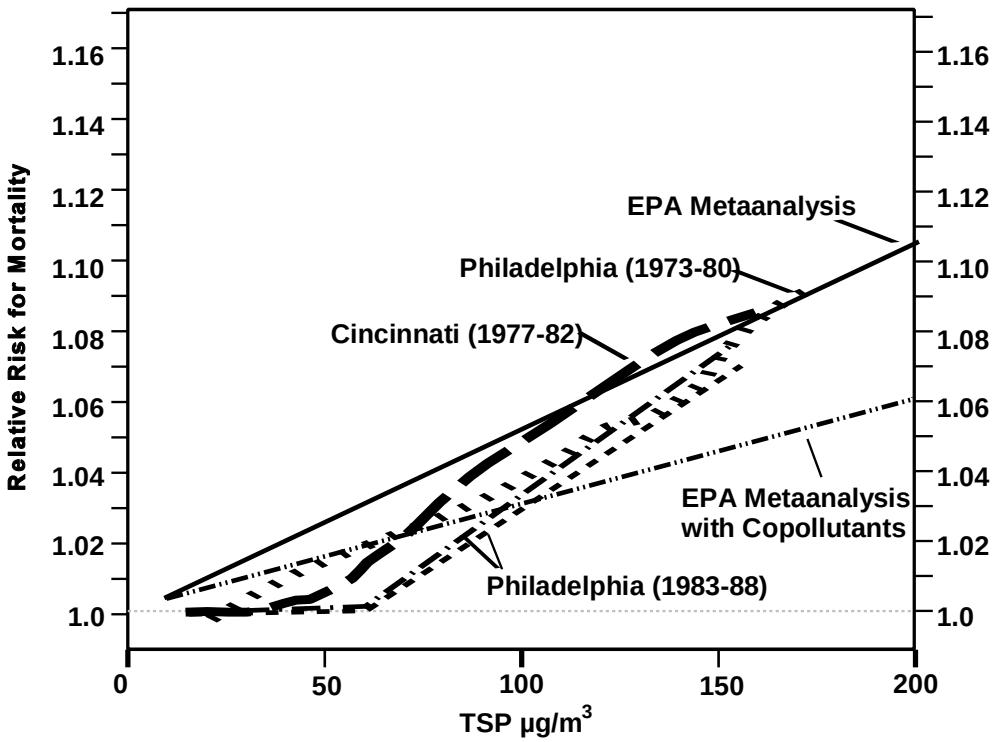

Figure 13-6. Comparison of smoothed nonlinear and linear mathematical models for relative risk of total mortality associated with short-term TSP exposure. Curves show smoothed nonparametric models for Philadelphia (based on Schwartz 1994b and for Cincinnati (based on Schwartz, 1994a), and piecewise linear models for Philadelphia (based on Cifuentes and Lave, 1996). Solid curve shows linear model from EPA metaanalysis using studies with no copollutants, dash-dot curve shows linear model from EPA metaanalysis using studies with SO_2 as a copollutant (described in Chapter 12).

with copollutants (Philadelphia 1983 to 1988, EPA metaanalysis) show some tendency for a linear model to over estimate mortality at low concentrations and to underestimate mortality at higher concentrations. The differences between linear and nonlinear models are sometimes statistically significant (Samet et al., 1995). Not enough comparisons are available to determine whether nonlinear models may be needed for PM_{10} or $PM_{2.5}$ concentration-effect relationships, but some assessments reported for Birmingham (Schwartz, 1994g) and Utah Valley (Pope and Kalkstein, 1996) find no significant improvement by fitting LOESS models instead of a linear model. Additional tests of the adequacy of the additive linear model for PM and its copollutants

would be desirable. The additive linear model and the corresponding RR estimates appear adequate for assessments of PM_{10} and $PM_{2.5}$ effects.

13.7 SUMMARY AND CONCLUSIONS

The chemical and physical differences between fine-mode and coarse-mode particles have important implications for evaluation of the health and welfare effects of such particles as distinct pollutant subclasses. For example, as discussed in Section 13.3, the differences in removal of fine and coarse particles from air streams leads to differences in respiratory tract deposition, although both fine and coarse particles penetrate into and deposit in all regions of the respiratory tract. According to the available empirical evidence and deposition models, particles above 15 μm are largely removed by impaction in the nose, throat and larynx. The efficiency of removal in this region falls as particle size decreases from 10μm to 1μm d_{ae} and reaches a minimum between 0.5 and 0.1 μm d_{ae}. As the particle size decreases below 0.1 μm d_{ae}, the removal efficiency increases again due to diffusion of the very small particles to surfaces. The larger particles in the coarse fraction are deposited more in the tracheobronchial region (TB) and, as particle size decreases, TB deposition decreases and alveolar deposition increases, reaching a peak between approximately 1 and 5 μm d_{ae}. Both TB and alveolar deposition reach a minimum in the accumulation-mode size range between 0.5 and 1.0 μm d_{ae} with alveolar deposition being greater than TB deposition. For particle sizes below 0.5 μm d_{ae}, both TB and alveolar deposition increase due to diffusion and reach a peak below 0.1 μm.

Our current understanding of the toxicology of ambient particulate matter suggests that fine and coarse particles may have different biological effects. For example, as discussed more fully in Chapter 11 and Section 13.5, differences in chemical composition of fine and coarse particles lead to the prediction of different biological effects. Acids, metals which generate hydroxyl radicals and reactive oxidant species in the lung, and dissolved reactive species may all be carried into the respiratory tract by fine particles. On other hand, silica (which may produce a distinctive lung pathology) and biological materials such as spores, pollens, bacteria, and other biological fragments which may produce immune responses are found primarily among coarse-mode particles, many of which may be larger than 10 μm. Some epidemiology studies tend to show stronger associations with fine particle indicators than with coarse particles.

However, clear differentiation between $PM_{2.5}$ and PM_{10} is difficult from currently available analyses and is complicated by the fact that $PM_{2.5}$ is part of PM_{10}. Direct assessment of coarse PM effects (i.e., $PM_{15/10}$-$PM_{2.5}$) is especially limited in available epidemiologic studies.

The evidence for PM-related effects from epidemiologic studies is fairly strong, with most studies showing increases in mortality, hospital admissions, respiratory symptoms, and pulmonary function decrements associated with several PM indices. These epidemiologic findings cannot be wholly attributed to inappropriate or incorrect statistical methods, misspecification of concentration-effect models, biases in study design or implementation, measurement errors in health endpoint, pollution exposure, weather, or other variables, nor confounding of PM effects with effects of other factors. While the results of the epidemiology studies should be interpreted cautiously, they nonetheless provide ample reason to be concerned that there are detectable human health effects attributable to PM at levels below the current NAAQS.

There is considerable agreement among different studies that the elderly are particularly susceptible to effects from both short-term and long-term exposures to PM, especially if they have underlying respiratory or cardiac disease. These effects include increases in mortality and increases in hospital admissions. Children, especially those with respiratory diseases, may also be susceptible to pulmonary function decrements associated with exposure to PM or acid aerosols. Respiratory symptoms and reduced activity days have also been associated with PM exposures in some studies.

A number of studies using multiple air pollutants as predictors of health effects have not completely resolved the role of PM as an independent causal factor. PM concentrations are often correlated with concentrations of other pollutants, in part because of common emissions patterns and in part because of weather patterns. There are seasonal differences within any community, however, and differences exist among various communities that allow at least some separation of PM effects from those of other pollutants. Unfortunately, most of the analyses of multiple pollutants within cities have used additive linear models that may not adequately characterize the interactions among pollutants, so that confident assignment of specific fractions of variation in health endpoints to specific air pollutants may still require additional study.

Within the overall PM complex, the indices that have been most consistently associated with health endpoints are fine particles (indexed by BS, COH, and $PM_{2.5}$), inhalable particles

(PM_{10} or PM_{15}), and sulfate ($SO_4^{=}$). Less consistent relationships have been observed for TSP, strong acidity (H^+), and coarse PM ($PM_{10-2.5}$). For reasons discussed above, none of these indices can completely be ruled out as a biologically relevant indicator of PM exposure.

Based on current evidence from epidemiologic, controlled human, human occupational, and laboratory animal studies, no conclusions can be reached regarding the specific chemical components of PM_{10} that may have the strongest biologic activity. Various subclasses of PM have been considered including acid aerosols, bioaerosols, metals (including transition metals), and insoluble ultrafine particles. On the basis of currently available information, none of these can be specifically implicated as the sole or even primary cause of specific morbidity and mortality effects.

Recent analyses have substantiated the previous selection of PM_{10} as an indicator of particle-related health effects. The strong and consistent association of mortality and various morbidity endpoints with PM_{10} exposure clearly demonstrates that this indicator of inhalable particle mass and the associated PM standard are appropriate for the protection of public health.

There is evidence that older adults with cardiopulmonary disease are more likely to be impacted by PM-related health effects (including mortality) than are healthy young adults. The likelihood of ambient fine mode particles being significant contributors to PM-related mortality and morbidity among this elderly population is bolstered by: (1) the more uniform distribution of fine particles across urban areas and their well-correlated variation from site to site within a given city; (2) the penetration of ambient particles to indoor environments (where many chronically ill elderly individuals can be expected to spend most of their time), and (3) the longer residence time of ambient fine particles in indoor air, enhancing the probability of indoor exposure to ambient fine particles more so than for indoor exposure to ambient coarse particles.

In addition to the above rather broad classification of elderly individuals (including ≈50% of adults over 65) as being at special risk, identification of other specific sensitive populations by age group or specific disease entity may also be warranted based on currently available analyses. These clearly include younger (i.e., < 65) individuals with acute or chronic respiratory disease (e.g., pneumonia, COPD, etc.) and/or cardiovascular diseases, current and former smokers (who account for about 80 to 85% of COPD deaths and many cardiovascular disease deaths), and possibly young children in regard to acute pulmonary function decrements being induced by low level PM exposures.

The above-noted differences indicate that it would be appropriate to consider fine and coarse mode particles as separate subclasses of pollutants. For this reason it would be desirable to monitor each class separately. Because fine and coarse particles are derived from different sources, it is also necessary to quantify ambient levels of fine and coarse particles separately in order to plan effective control strategies.

REFERENCES

AIRS, Aerometric Information Retrieval System [database]. (1995) Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards.

Abbey, D. E. (1994) Incidence of respiratory symptoms and chronic disease in a non-smoking population as a function of long-term cumulative exposure to ambient air pollutants (Adventist health study of smog follow-up study): final report, volume 1. Sacramento, CA: California Air Resources Board; report no. ARB-R-94/542. Available from: NTIS, Springfield, VA; PB94-218740.

Abbey, D. E.; Mills, P. K.; Petersen, F. F.; Beeson, W. L. (1991) Long-term ambient concentrations of total suspended particulates and oxidants as related to incidence of chronic disease in California Seventh-Day Adventists. Environ. Health Perspect. 94: 43-50.

Abbey, D. E.; Lebowitz, M. D.; Mills, P. K.; Petersen, F. F.; Beeson, W. L.; Burchette, R. J. (1995a) Long-term ambient concentrations of particulates and oxidants and development of chronic disease in a cohort of nonsmoking California residents. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 19-34.

Abbey, D. E.; Ostro, B. E.; Petersen, F.; Burchette, R. J. (1995b) Chronic respiratory symptoms associated with estimated long-term ambient concentrations of fine particulates less than 2.5 microns in aerodynamic diameter (PM2.5) and other air pollutants. J. Exp. Anal. Environ. Epidemiol. 5: 137-159.

Abbey, D. E.; Ostro, B. E.; Fraser, G.; Vancuren, T.; Burchette, R. J. (1995c) Estimating fine particulates less that 2.5 microns in aerodynamic diameter (PM2.5) from airport visibility data in California. J. Exp. Anal. Environ. Epidemiol. 5: 161-180.

Ackermann-Liebrich, U.; Leuenberger, P.; Schwartz, J.; Schindler, C.; Monn, C.; Bolognini, B.; Bongard, J. P.; Brändli, O.; Domenighetti, G.; Elsasser, S.; Grize, L.; Karrer, W.; Keller, R.; Keller-Wossidlo, H.; Künzli, N.; Martin, B. W.; Medici, T. G.; Perruchoud, A. P.; Schöni, M. H.; Tschopp, J. M.; Villiger, B.; Wüthrich, B.; Zellweger, J. P.; Zemp, E. (1996) Lung function and long term exposure to air pollutants in Switzerland. Am. J. Respir. Crit. Care Med.: submitted.

American Thoracic Society. (1995) Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease: definitions, epidemiology, pathopysiology, diagnosis, and staging. Am. J. Respir. Crit. Care Med. 152(suppl.): S78-S83.

Andersen, M. E.; Krishnan, K.; Conolly, R. B.; McClellan, R. O. (1992) Mechanistic toxicology research and biologically-based modeling: partners for improving quantitative risk assessments. CIIT Activities 12 (1): 1-7.

Anderson, P. J.; Wilson, J. D.; Hiller, F. C. (1990) Respiratory tract deposition of ultrafine particles in subjects with obstructive or restrictive lung disease. Chest 97: 1115-1120.

Anderson, K. R.; Avol, E. L.; Edwards, S. A.; Shamoo, D. A.; Peng, R.-C.; Linn, W. S.; Hackney, J. D. (1992) Controlled exposures of volunteers to respirable carbon and sulfuric acid aerosols. J. Air Waste Manage. Assoc. 42: 770-776.

Antó, J. M.; Sunyer, J. (1990) Epidemiologic studies of asthma epidemics in Barcelona. Chest 90(suppl.): 185S-190S.

Avol, E. L.; Linn, W. S.; Shamoo, D. A.; Anderson, K. R.; Peng, R.-C.; Hackney, J. D. (1990) Respiratory responses of young asthmatic volunteers in controlled exposures to sulfuric acid aerosol. Am. Rev. Respir. Dis. 142: 343-348.

Ayres, J. G. (1986) Trends in asthma and hay fever in general practice in the United Kingdom 1976-83. Thorax 41: 111-116.

Bates, D. V. (1989) Overview on characterizing study groups and their responses. In: Utell, M. J.; Frank, R., eds. Susceptibility to inhaled pollutants: [papers presented at the conference]; October 1987; Williamsburg, VA. Pittsburgh, PA: American Society for Testing and Materials; pp; 55-56. (ASTM special technical publication no. STP 1024).

Bates, D. V. (1992) Health indices of the adverse effects of air pollution: the question of coherence. Environ. Res. 59: 336-349.

Bates, D. V.; Sizto, R. (1987) Air pollution and hospital admissions in southern Ontario: the acid summer haze effect. Environ. Res. 43: 317-331.

Bates, D. V.; Sizto, R. (1989) The Ontario Air Pollution study: identification of the causative agent. Environ. Health Perspect. 79: 69-72.

Bates, D. V.; Macklen, P. T.; Christie, R. V. (1971) Respiratory function in disease. 2nd ed. Philadelphia, PA: W. B. Saunders; p. 584.

Benenson, A. S., ed. (1990) Control of communicable diseases in man. 15th ed. Washington, DC: American Public Health Association; pp. 330-339.

Bennett, W. D.; Zeman, K. L.; Kim, C.; Mascarella, J. (1996) Enhanced deposition of fine particles in COPD patients spontaneously breathing at rest. Submitted.

Bobak, M.; Leon, D. A. (1992) Air pollution and infant mortality in the Czech Republic, 1986-1988. Lancet (8826): 1010-1014.

Bock, N.; Lippmann, M.; Lioy, P.; Munoz, A.; Speizer, F. E. (1985) The effects of ozone on the pulmonary function of children. In: Lee, S. D., ed. Evaluation of the scientific basis for ozone/oxidants standards: proceedings of an APCA international specialty conference; November 1984; Houston, TX. Pittsburgh, PA: Air Pollution Control Association; pp. 297-308. (APCA international specialty conference transactions: TR-4).

Brand, P.; Gebhart, J.; Below, M.; Georgi, B.; Heyder, J. (1991) Characterization of environmental aerosols on Heligoland Island. Atmos. Environ. Part A 25: 581-585.

Brand, P.; Ruob, K.; Gebhart, J. (1992) Performance of a mobile aerosol spectrometer for an *in situ* characterization of environmental aerosols in Frankfurt city. Atmos. Environ. Part A 26: 2451-2457.

Burnett, R. T.; Dales, R. E.; Raizenne, M. E.; Krewski, D.; Summers, P. W.; Roberts, G. R.; Raad-Young, M.; Dann, T.; Brook, J. (1994) Effects of low ambient levels of ozone and sulfates on the frequency of respiratory admissions to Ontario hospitals. Environ. Res. 65: 172-194.

Burnett, R. T.; Dales, R.; Krewski, D.; Vincent, R.; Dann, T.; Brook, J. R. (1995) Associations between ambient particulate sulfate and admissions to Ontario hospitals for cardiac and respiratory diseases. Am. J. Epidemiol. 142: 15-22.

Burton, R. M.; Suh, H. H.; Koutrakis, P. (1996) Spatial variation in particulate concentrations within metropolitan Philadelphia. Environ. Sci. Technol. 30: 400-407.

Castellani, C. M. (1993) Characterization of the atmospheric aerosol in an urban area and the vicinity of a main highway. In: ENEA Environment Department meetings and seminars; Bologna and Rome, Italy. INTO 7(93): 35-55.

Chapman, R. S.; Calafiore, D. C.; Hasselblad, V. (1985) Prevalence of persistent cough and phlegm in young adults in relation to long-term ambient sulfur oxide exposure. Am. Rev. Respir. Dis. 132: 261-267.

Chen, L. C.; Miller, P. D.; Amdur, M. O.; Gordon, T. (1992) Airway hyperresponsiveness in guinea pigs exposed to acid-coated ultrafine particles. J. Toxicol. Environ. Health 35: 165-174.

Chen, L. C.; Wu, C. Y.; Qu, Q. S.; Schlesinger, R. B. (1995) Number concentration and mass concentration as determinants of biological response to inhaled irritant particles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 577-588.

Chestnut, L. G.; Schwartz, J.; Savitz, D. A.; Burchfiel, C. M. (1991) Pulmonary function and ambient particulate matter: epidemiological evidence from NHANES I. Arch. Environ. Health 46: 135-144.

Cifuentes, L.; Lave, L. B. (1996) Association of daily mortality and air pollution in Philadelphia, 1983-1988. J. Air Waste Manage. Assoc.: in press.

Dahl, A. R.; Schlesinger, R. B.; Heck, H. D' A.; Medinsky, M. A.; Lucier, G. W. (1991) Comparative dosimetry of inhaled materials: differences among animal species and extrapolation to man. Fundam. Appl. Toxicol. 16: 1-13.

Dahlqvist, M.; Alexandersson, R.; Andersson, B.; Andersson, K.; Kolmodin-Hedman, B.; Malker, H. (1992) Exposure to ski-wax smoke and health effects in ski waxers. Appl. Occup. Environ. Hyg. 7: 689-693.

Dassen, W.; Brunekreef, B.; Hoek, G.; Hofschreuder, P.; Staatsen, B.; De Groot, H.; Schouten, E.; Biersteker, K. (1986) Decline in children's pulmonary function during an air pollution episode. J. Air Pollut. Control Assoc. 36: 1223-1227.

Davis, R. M.; Novotny, T. E. (1989) The epidemiology of cigarette smoking and its impact on chronic obstructive pulmonary disease. In: The rise in chronic obstructive pulmonary disease mortality. Am. Rev. Respir. Dis. 140(suppl.): S82-S84.

Delfino, R. J.; Becklake, M. R.; Hanley, J. A. (1994) The relationship of urgent hospital admissions for respiratory illnesses to photochemical air pollution levels in Montreal. Environ. Res. 67: 1-19.

Dice, J. F. (1993) Cellular and molecular mechanisms of aging. Physiol. Rev. 73: 149-159.

Dockery, D. W.; Speizer, F. E.; Stram, D. O.; Ware, J. H.; Spengler, J. D.; Ferris, B. G., Jr. (1989) Effects of inhalable particles on respiratory health of children. Am. Rev. Respir. Dis. 139: 587-594.

Dockery, D. W.; Schwartz, J.; Spengler, J. D. (1992) Air pollution and daily mortality: associations with particulates and acid aerosols. Environ. Res. 59: 362-373.

Dockery, D. W.; Pope, C. A., III; Xu, X.; Spengler, J. D.; Ware, J. H.; Fay, M. E.; Ferris, B. G., Jr.; Speizer, F. E. (1993) An association between air pollution and mortality in six U.S. cities. N. Engl. J. Med. 329: 1753-1759.

Dockery, D. W.; Cunningham, J.; Damokosh, A. I.; Neas, L. M.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Raizenne, M.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: respiratory symptoms. Environ. Health Perspect: in press.

Dodge, R.; Solomon, P.; Moyers, J.; Hayes, C. (1985) A longitudinal study of children exposed to sulfur oxides. Am. J. Epidemiol. 121: 720-736.

Dusseldorp, A.; Kruize, H.; Brunekreef, B.; Hofschreuder, P.; de Meer, G.; van Oudvorst, A. B. (1994) Associations of PM10 and airborne iron with respiratory health of adults living near a steel factory. Am. J. Respir. Crit. Care Med. 152: 1932-1939.

Ferin, J.; Oberdörster, G.; Penney, D. P.; Soderholm, S. C.; Gelein, R.; Piper, H. C. (1990) Increased pulmonary toxicity of ultrafine particles? I. Particle clearance, translocation, morphology. J. Aerosol. Sci. 21: 381-384.

Folkow, B.; Svanborg, A. (1993) Physiology of cardiovascular aging. Physiol. Rev. 73: 725-764.

Frampton, M. W.; Voter, K. Z.; Morrow, P. E.; Roberts, N. J., Jr.; Culp, D. J.; Cox, C.; Utell, M. J. (1992) Sulfuric acid aerosol exposure in humans assessed by bronchoalveolar lavage. Am. Rev. Respir. Dis. 146: 626-632.

Gergen, P. J.; Weiss, K. B. (1992) The increasing problem of asthma in the United States. Am. Rev. Respir. Dis. 146: 823-824.

Glikson, M.; Rutherford, S. Simpson, R. W.; Mitchell, C. A.; Yago, A. (1995) Microscopic and submicron components of atmospheric particulate matter during high asthma periods in Brisbane, Queensland, Australia. Atmos. Environ. 29: 549-562.

Goldstein, M.; Weiss, H.; Wade, K.; Penek, J.; Andrews, L.; Brandt-Rauf, P. (1987) An outbreak of fume fever in an electronics instrument testing laboratory. J. Occup. Med. 29: 746-749.

Gordian, M. E.; Morris, S.; Özkaynak, H.; Xue, J.; Spengler, J. (1995) Particulate air pollution and respiratory disease in Anchorage, Alaska. In: Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; pp. 143-166. (A&WMA publication VIP-49).

Gordian, M. E.; Ozkaynak, H.; Xue, J.; Morris, S. S.; Spengler, J. D. (1996) Particulate air pollution and respiratory disease in Achorage, Alaska. Environ. Health Perspect. 104: 290-297.

Hatch, V.; Hauser, R.; Hayes, G. B.; Stearns, R.; Christiani, D.; Godleski, J. J. (1994) Detection of ultrafine particles in the lung macrophages of healthy people. In: Bailey, G. W.; Garratt-Reed, A. J., eds. Proceedings fifty-second annual meeting, Microscopy Society of America, twenty-ninth annual meeting, Microbeam Analysis Society; August; New Orleans, LA. San Francisco, CA: San Francisco Press, Inc.; pp. 1004-1005.

Hefflin, B. J.; Jalaludin, B.; McClure, E.; Cobb, N.; Johnson, C. A.; Jecha, L.; Etzel, R. A. (1994) Surveillance for dust storms and respiratory diseases in Washington State, 1991. Arch. Environ. Health 49: 170-174.

Hoek, G.; Brunekreef, B. (1993) Acute effects of a winter air pollution episode on pulmonary function and respiratory symptoms of children. Arch. Environ. Health 48: 328-335.

Hoek, G.; Brunekreef, B. (1994) Effects of low-level winter air pollution concentrations on respiratory health of Dutch children. Environ. Res. 64: 136-150.

Hoek, G.; Brunekreef, B. (1995) Effect of photochemical air pollution on acute respiratory symptoms in children. Am. J. Respir. Crit. Care Med. 151: 27-32.

Horvath, S. M.; Folinsbee, L. J.; Bedi, J. F. (1987) Combined effect of ozone and sulfuric acid on pulmonary function in man. Am. Ind. Hyg. Assoc. J. 48: 94-98.

International Commission on Radiological Protection. (1994) Human respiratory tract model for radiological protection: a report of a task group of the International Commission on Radiological Protection. Oxford, United Kingdom: Elsevier Science Ltd. (ICRP publication 66; Annals of the ICRP: v. 24, nos. 1-3).

Ito., K.; Thurston, G. D. (1996) Daily PM10/mortality associations: an investigation of at-risk sub-populations. J. Exposure Anal. Environ. Epidemiol.: in press.

Ito, K.; Thurston, G. D.; Hayes, C.; Lippmann, M. (1993) Associations of London, England, daily mortality with particulate matter, sulfur dioxide, and acidic aerosol pollution. Arch. Environ. Health 48: 213-220.

Ito, K.; Kinney, P.; Thurston, G. D. (1995) Variations in PM-10 concentrations within two metropolitan areas and their implications for health effects analyses. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 735-745.

Jedrychowski, W.; Krzyżanowski, M. (1989) Ventilatory lung function and chronic chest symptoms among the inhabitants of urban areas with various levels of acid aerosols: prospective study in Cracow. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 101-107.

Johnson, K. G.; Loftsgaarden, D. O.; Gideon, R. A. (1982) The effects of Mount St. Helens volcanic ash on the pulmonary function of 120 elementary school children. Am. Rev. Respir. Dis. 126: 1066-1069.

Johnson, K. G.; Gideon, R. A.; Loftsgaarden, D. O. (1990) Montana Air Pollution Study: children's health effects. J. Off. Stat. 5: 391-407.

Kenney, R. A., ed. (1989) Physiology of aging: a synopsis. Chicago, IL: Year Book Medical Publishers, Inc.

Kim, C. S.; Lewars, G. A.; Sackner, M. A. (1988) Measurement of total lung aerosol deposition as an index of lung abnormality. J. Appl. Physiol. 64: 1527-1536.

Kinney, P. L.; Ito, K.; Thurston, G. D. (1995) A sensitivity analysis of mortality/PM_{10} associations in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 59-69.

Koenig, J. Q.; Covert, D. S.; Pierson, W. E. (1989) Effects of inhalation of acidic compounds on pulmonary function in allergic adolescent subjects. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 173-178.

Koenig, J. Q.; Larson, T. V.; Hanley, Q. S.; Rebolledo, V.; Dumler, K.; Checkoway, H.; Wang, S.-Z.; Lin, D.; Pierson, W. E. (1993) Pulmonary function changes in children associated with fine particulate matter. Environ. Res. 63: 26-38.

Koutrakis, P.; Briggs, S. L. K.; Leaderer, B. P. (1992) Source apportionment of indoor aerosols in Suffolk and Onondaga Counties, New York. Environ. Sci. Technol. 26: 521-527.

Kunst, A. E.; Looman, C. W. N.; Mackenbach, J. P. (1993) Outdoor air temperature and mortality in the Netherlands: a time-series analysis. Am. J. Epidemiol. 137: 331-341.

Lacey, J.; Dutkiewicz, J. (1994) Bioaerosols and occupational lung disease. J. Aerosol. Sci. 25: 1371-1404.

Lakatta, E. G. (1993) Cardiovascular regulatory mechanisms in advanced age. Physiol. Rev. 73: 413-467.

Lamm, S. H.; Hall, T. A.; Engel, A.; Rueter, F. H.; White, L. D. (1994) PM_{10} particulates: are they the major determinant of pediatric respiratory admissions in Utah County, Utah (1985-1989). In: Dodgson, J.; McCallum, R. I., eds. Inhaled particles VII: proceedings of an international symposium; September 1991; Edinburgh, United Kingdom. Ann. Occup. Hyg. 38(suppl. 1): 969-972.

Lang, D. M.; Polansky, M. (1994) Patterns of asthma mortality in Philadelphia from 1969 to 1991. N. Engl. J. Med. 331: 1542-1546.

Lawther, P. J.; Waller, R. E.; Henderson, M. (1970) Air pollution and exacerbations of bronchitis. Thorax 25: 525-539.

Li, Y.; Roth, H. D. (1995) Daily mortality analysis by using different regression models in Philadelphia County, 1973-1990. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 45-58.

Lighthart, B.; Mohr, A. J. (1994) Atmospheric microbial aerosols: theory and applications. New York, NY: Chapman & Hall.

Lighthart, B.; Stetzenbach, L. D. (1994) Distribution of microbial bioaerosol. In: Lighthart, B.; Mohr, A. J., eds. Atmospheric microbial aerosols: theory and applications. New York, NY: Chapman & Hall; pp. 68-98.

Lipfert, F. W. (1993) Community air pollution and mortality: analysis of 1980 data from US metropolitan areas. I. Particulate air pollution. Upton, NY: U.S. Department of Energy, Brookhaven National Laboratory; report no. BNL 48446-R.

Lipfert, F. W. (1995) Estimating air pollution-mortality risks from cross-sectional studies: prospective vs. ecologic study designs. In: Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; pp. 78-102. (A&WMA publication VIP-49).

Lipfert, F. W.; Wyzga, R. E. (1995) Air pollution and mortality: issues and uncertainties. Presented at: 88th annual meeting & exhibition of the Air & Waste Management Association; June; San Antonio, TX. Pittsburgh, PA: Air & Waste Management Association; paper no. 95-MP19.03.

Lipfert, F. W.; Malone, R. G.; Daum, M. L.; Mendell, N. R.; Yang, C.-C. (1988) A statistical study of the macroepidemiology of air pollution and total mortality. Upton, NY: U.S. Department of Energy, Brookhaven National Laboratory; report no. BNL-52122.

Lippmann, M.; Ito, K. (1995) Separating the effects of temperature and season on daily mortality from those of air pollution in London: 1965-1972. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 85-97.

Logan, W. P. D. (1953) Mortality in the London fog incident, 1952. Lancet (Feb. 14): 336-339.

Lyon, J. L.; Mori, M.; Gao, R. (1995) Is there a causal association between excess mortality and exposure to PM-10 air pollution? Additional analyses by location, year, season and cause of death. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 603-614.

Mackay, T. W.; Wathen, C. G.; Sudlow, M. F.; Elton, R. A.; Caulton, E. (1992) Factors affecting asthma mortality in Scotland. Scott. Med. J. 37: 5-7.

Madelin, T. M. (1994) Fungal aerosols: a review. J. Aerosol Sci. 25: 1405-1412.

Matthias-Maser, S.; Jaenicke, R. (1994) Examination of atmospheric bioaerosol particles with radii > 0.2 μm. J. Aerosol Sci. 25: 1605-1613.

Mauderly, J. L.; Bice, D. E.; Cheng, Y. S.; Gillett, N. A.; Griffith, W. C.; Henderson, R. F.; Pickrell, J. A.; Wolff, R. K. (1990) Influence of preexisting pulmonary emphysema on susceptibility of rats to diesel exhaust. Am. Rev. Respir. Dis. 141: 1333-1341.

Miller, F. J.; Angilvel, S.; Ménache, M. G.; Asgharian, B.; Gerrity, T. R. (1995) Dosimetric issues relating to particulate toxicity. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 615-632.

Moolgavkar, S. H.; Luebeck, E. G.; Hall, T. A.; Anderson, E. L. (1995) Air pollution and daily mortality in Philadelphia. Epidemiology 6: 476-484.

Morrow, P. E. (1988) Possible mechanisms to explain dust overloading of the lungs. Fundam. Appl. Toxicol. 10: 369-384.

Morrow, P. E.; Utell, M. J.; Bauer, M. A.; Speers, D. M.; Gibb, F. R. (1994) Effects of near ambient levels of sulphuric acid aerosol on lung function in exercising subjects with asthma and chronic obstructive pulmonary disease. In: Dodgson, J.; McCallum, R. I., eds. Inhaled particles VII: proceedings of an international symposium; September 1991; Edinburgh, United Kingdom. Ann. Occup. Hyg. 38(suppl. 1): 933-938.

National Center for Health Statistics. (1993) Advance report of final mortality statistics, 1991. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention. (Monthly vital statistics report: v. 42, no. 2, suppl.).

National Center for Health Statistics. (1994) Current estimates from the National Health Interview Survey, 1992. Hyattsville, MD: U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control and Prevention; DHHS publication no. (PHS) 94-1517. (Data from the National Health Survey: series 10, no. 189).

National Center for Health Statistics. (1996) Advance report of final mortality statistics, 1993. Mon. Vital Stat. Rep. 44 (no. 7).

National Research Council. (1987) Pharmacokinetics in risk assessment: drinking water and health, v. 8. Washington, DC: National Academy Press.

Neas, L. M.; Dockery, D. W.; Koutrakis, P.; Tollerud, D. J.; Speizer, F. E. (1995) The association of ambient air pollution with twice daily peak expiratory flow rate measurements in children. Am. J. Epidemiol. 141: 111-122.

O'Hollaren, M. T.; Yunginger, J. W.; Offord, K. P.; Somers, M. J.; O'Connell, E. J.; Ballard, D. J.; Sachs, M. I. (1991) Exposure to an aeroallergen as a possible precipitating factor in respiratory arrest in young patients with asthma. N. Engl. J. Med. 324: 359-363.

Oberdörster, G.; Ferin, J.; Gelein, R.; Soderholm, S. C.; Finkelstein, J. (1992a) Role of the alveolar macrophage in lung injury: studies with ultrafine particles. Environ. Health Perspect. 97: 193-199.

Oberdörster, G.; Ferin, J.; Morrow, P. E. (1992b) Volumetric loading of alveolar macrophages (AM): a possible basis for diminished AM-mediated particle clearance. Exp. Lung Res. 18: 87-104.

Oberdörster, G.; Ferin, J.; Lehnert, B. E. (1994) Correlation between particle size, in vivo particle persistence, and lung injury. Environ. Health Perspect. 102(suppl. 5): 173-179.

Oberdörster, G.; Gelein, R. M.; Ferin, J.; Weiss, B. (1995a) Association of particulate air pollution and acute mortality: involvement of ultrafine particles? In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 111-124.

Oberdörster, G.; Ferin, J.; Gelein, R.; Mercer, P.; Corson, N.; Godleski, J. (1995b) Low-level ambient air particulate levels and acute mortality/morbidity: studies with ultrafine Teflon® particles. Am. J. Respir. Crit. Care Med. 151(suppl.): A66.

Ostro, B. D.; Lipsett, M. J.; Wiener, M. B.; Selner, J. C. (1991) Asthmatic responses to airborne acid aerosols. Am. J. Public Health 81: 694-702.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Krupnick, A.; Harrington, W. (1993) Air pollution and respiratory morbidity among adults in Southern California. Am. J. Epidemiol. 137: 691-700.

Ostro, B. D.; Lipsett, M. J.; Mann, J. K.; Braxton-Owens, H.; White, M. C. (1995) Air pollution and asthma exacerbations among African-American children in Los Angeles. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 711-722.

Ostro, B.; Sanchez, J. M.; Aranda, C.; Eskeland, G. S. (1996) Air pollution and mortality: results from a study of Santiago, Chile. In: Lippmann, M., ed. Papers from the ISEA-ISEE annual meeting; September 1994; Research Triangle Park, NC. J. Exposure Anal. Environ. Epidemiol.: in press.

Özkaynak, H.; Thurston, G. D. (1987) Associations between 1980 U.S. mortality rates and alternative measures of airborne particle concentration. Risk Anal. 7: 449-461.

Perry, G. B.; Chai, H.; Dickey, D. W.; Jones, R. H.; Kinsman, R. A.; Morrill, C. G.; Spector, S. L.; Weiser, P. C. (1983) Effects of particulate air pollution on asthmatics. Am. J. Public Health 73: 50-56.

Pönkä, A. (1991) Asthma and low level air pollution in Helsinki. Arch. Environ. Health 46: 262-270.

Pope, C. A., III. (1989) Respiratory disease associated with community air pollution and a steel mill, Utah Valley. Am. J. Public Health 79: 623-628.

Pope, C. A., III. (1991) Respiratory hospital admissions associated with PM_{10} pollution in Utah, Salt Lake, and Cache Valleys. Arch. Environ. Health 46: 90-97.

Pope, C. A., III. (1994) Particulate pollution and mortality in Utah valley. Prepared for: Critical evaluation workshop on particulate matter—mortality epidemiology studies; November; Raleigh, NC. Provo, UT: Brigham Young University.

Pope, C. A., III; Dockery, D. W. (1992) Acute health effects of PM_{10} pollution on symptomatic and asymptomatic children. Am. Rev. Respir. Dis. 145: 1123-1128.

Pope, C. A., III; Kalkstein, L. S. (1996) Synoptic weather modeling and estimates of the exposure-response relationship between daily mortality and particulate air pollution. Environ. Health Perspect. 104: in press.

Pope, C. A., III; Kanner, R. E. (1993) Acute effects of PM_{10} pollution on pulmonary function of smokers with mild to moderate chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 147: 1336-1340.

Pope, C. A., III; Dockery, D. W.; Spengler, J. D.; Raizenne, M. E. (1991) Respiratory health and PM_{10} pollution: a daily time series analysis. Am. Rev. Respir. Dis. 144: 668-674.

Pope, C. A., III; Schwartz, J.; Ransom, M. R. (1992) Daily mortality and PM_{10} pollution in Utah valley. Arch. Environ. Health 47: 211-217.

Pope, C. A., III; Thun, M. J.; Namboodiri, M. M.; Dockery, D. W.; Evans, J. S.; Speizer, F. E.; Heath, C. W., Jr. (1995) Particulate air pollution as a predictor of mortality in a prospective study of U.S. adults. Am. J. Respir. Crit. Care Med. 151: 669-674.

Raizenne, M. E.; Burnett, R. T.; Stern, B.; Franklin, C. A.; Spengler, J. D. (1989) Acute lung function responses to ambient acid aerosol exposures in children. Environ. Health Perspect. 79: 179-185.

Raizenne, M.; Neas, L. M.; Damokosh, A. I.; Dockery, D. W.; Spengler, J. D.; Koutrakis, P.; Ware, J. H.; Speizer, F. E. (1996) Health effects of acid aerosols on North American children: pulmonary function. Environ. Health Perspect.: accepted.

Roemer, W.; Hoek, G.; Brunekreef, B. (1993) Effect of ambient winter air pollution on respiratory health of children with chronic respiratory symptoms. Am. Rev. Respir. Dis. 147: 118-124.

Saldiva, P. H. N.; Lichtenfels, A. J. F. C.; Paiva, P. S. O.; Barone, I. A.; Martins, M. A.; Massad, E.; Pereira, J. C. R.; Xavier, V. P.; Singer, J. M.; Böhm, G. M. (1994) Association between air pollution and mortality due to respiratory diseases in children in São Paulo, Brazil: a preliminary report. Environ. Res. 65: 218-225.

Saldiva, P. H. N.; Pope, C. A., III; Schwartz, J.; Dockery, D. W.; Lichtenfels, A. J.; Salge, J. M.; Barone, I.; Böhm, G. M. (1995) Air pollution and mortality in elderly people: a time-series study in São Paulo, Brazil. Arch. Environ. Health 50: 159-163.

Salem, H.; Gardner, D. E. (1994) Health aspects of bioaerosols. In: Lighthart, B.; Mohr, A. J., eds. Atmospheric microbial aerosols: theory and applications. New York, NY: Chapman & Hall; pp. 304-330.

Samet, J. M.; Zeger, S. L.; Berhane, K. (1995) The association of mortality and particulate air pollution. In: Particulate air pollution and daily mortality: replication and validation of selected studies, the phase I report of the particle epidemiology evaluation project [preprint]. Cambridge, MA: Health Effects Institute; pp. 1-104.

Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J. (1996a) Air pollution and mortality in Philadelphia, 1974-1988, report to the Health Effects Institute on phase IB: Particle Epidemiology Evaluation Project. Cambridge, MA: Health Effects Institute; accepted.

Samet, J. M.; Zeger, S. L.; Kelsall, J. E.; Xu, J.; Kalkstein, L. S. (1996b) Weather, air pollution and mortality in Philadelphia, 1973-1980, report to the Health Effects Institute on phase IB, Particle Epidemiology Evaluation Project. Cambridge, MA: Health Effects Institute; review draft.

Schulte, P. A. (1989) A conceptual framework for the validation and use of biologic markers. Environ. Res. 48: 129-144.

Schwartz, J. (1993) Air pollution and daily mortality in Birmingham, Alabama. Am. J. Epidemiol. 137: 1136-1147.

Schwartz, J. (1994a) Total suspended particulate matter and daily mortality in Cincinnati, Ohio. Environ. Health Perspect. 102: 186-189.

Schwartz, J. (1994b) Air pollution and daily mortality: a review and meta analysis. Environ. Res. 64: 36-52.

Schwartz, J. (1994c) What are people dying of on high air pollution days? Environ. Res. 64: 26-35.

Schwartz, J. (1994d) Air pollution and hospital admissions for the elderly in Detroit, Michigan. Am. J. Respir. Crit. Care Med. 150: 648-655.

Schwartz, J. (1994e) Air pollution and hospital admissions for the elderly in Birmingham, Alabama. Am. J. Epidemiol. 139: 589-598.

Schwartz, J. (1994f) PM_{10}, ozone, and hospital admissions for the elderly in Minneapolis, MN. Arch. Environ. Health 49: 366-374.

Schwartz, J. (1994g) Nonparametric smoothing in the analysis of air pollution and respiratory illness. Can. J. Stat. 22: 1-17.

Schwartz, J. (1995) Short term fluctuations in air pollution and hospital admissions of the elderly for respiratory disease. Thorax 50: 531-538.

Schwartz, J. (1996) Air pollution and hospital admissions for respiratory disease. Epidemiology 7: 20-28.

Schwartz, J.; Dockery, D. W. (1992a) Increased mortality in Philadelphia associated with daily air pollution concentrations. Am. Rev. Respir. Dis. 145: 600-604.

Schwartz, J.; Dockery, D. W. (1992b) Particulate air pollution and daily mortality in Steubenville, Ohio. Am. J. Epidemiol. 135: 12-19.

Schwartz, J.; Morris, R. (1995) Air pollution and hospital admissions for cardiovascular disease in Detroit, Michigan. Am. J. Epidemiol. 142: 23-35.

Schwartz, J.; Slater, D.; Larson, T. V.; Pierson, W. E.; Koenig, J. Q. (1993) Particulate air pollution and hospital emergency room visits for asthma in Seattle. Am. Rev. Respir. Dis. 147: 826-831.

Schwartz, J.; Dockery, D. W.; Neas, L. M.; Wypij, D.; Ware, J. H.; Spengler, J. D.; Koutrakis, P.; Speizer, F. E.; Ferris, B. G., Jr. (1994) Acute effects of summer air pollution on respiratory symptom reporting in children. Am. J. Respir. Crit. Care Med. 150: 1234-1242.

Schwartz, D. A.; Thorne, P. S.; Yagla, S. J.; Burmeister, L. F.; Olenchock, S. A.; Watt, J. L.; Quinn, T. J. (1995) The role of endotoxin in grain dust-induced lung disease. Am. J. Respir. Crit. Care Med. 152: 603-608.

Schwartz, J.; Dockery, D. W.; Neas, L. M. (1996a) Is daily mortality associated specifically with fine particles? J. Air Waste Manage. Assoc.: accepted.

Schwartz, J.; Spix, C.; Touloumi, G.; Bacharova, L.; Barumamdzadeh, T.; Le Tertre, A.; Piekarksi, T.; Ponce de Leon, A.; Ponka, A.; Rossi, G.; Saez, M.; Shouten, J. P. (1996b) Methodological issues in studies of air pollution and daily counts of deaths or hospital admissions. J. Epidemiol. Commun. Health: in press.

Seaton, A.; MacNee, W.; Donaldson, K.; Godden, D. (1995) Particulate air pollution and acute health effects. Lancet (8943): 176-178.

Seneff, M. G.; Wagner, D. P.; Wagner, R. P.; Zimmerman, J. E.; Knaus, W. A. (1995) Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. N. Engl. J. Med. 274: 1852-1857.

Silverman, F.; Hosein, H. R.; Corey, P.; Holton, S.; Tarlo, S. M. (1992) Effects of particulate matter exposure and medication use on asthmatics. Arch. Environ. Health 47: 51-56.

Speizer, F. E. (1989) Studies of acid aerosols in six cities and in a new multi-city investigation: design issues. Environ. Health Perspect. 79: 61-67.

Spektor, D. M.; Lippmann, M.; Lioy, P. J.; Thurston, G. D.; Citak, K.; James, D. J.; Bock, N.; Speizer, F. E.; Hayes, C. (1988) Effects of ambient ozone on respiratory function in active, normal children. Am. Rev. Respir. Dis. 137: 313-320.

Spektor, D. M.; Hofmeister, V. A.; Artaxo, P.; Brague, J. A. P.; Echelar, F.; Nogueira, D. P.; Hayes, C.; Thurston, G. D.; Lippmann, M. (1991) Effects of heavy industrial pollution on respiratory function in the children of Cubatao, Brazil: a preliminary report. Environ. Health Perspect. 94: 51-54.

Spix, C.; Heinrich, J.; Dockery, D.; Schwartz, J.; Völksch, G.; Schwinkowski, K.; Cöllen, C.; Wichmann, H. E. (1993) Air pollution and daily mortality in Erfurt, East Germany, 1980-1989. Environ. Health Perspect. 101: 518-526.

Stearns, R. C.; Murthy, G. G. K.; Skornik, W.; Hatch, V.; Katler, M.; Godleski, J. J. (1994) Detection of ultrafine copper oxide particles in the lungs of hamsters by electron spectroscopic imaging. In: Proceedings of international conference of electron microscopy, ICEM 13; July; Paris, France; pp. 763-764.

Stern, B.; Jones, L.; Raizenne, M.; Burnett, R.; Meranger, J. C.; Franklin, C. A. (1989) Respiratory health effects associated with ambient sulfates and ozone in two rural Canadian communities. Environ. Res. 49: 20-39.

Stern, B. R.; Raizenne, M. E.; Burnett, R. T.; Jones, L.; Kearney, J.; Franklin, C. A. (1994) Air pollution and childhood respiratory health: exposure to sulfate and ozone in 10 Canadian rural communities. Environ. Res. 66: 125-142.

Studnicka, M. J.; Frischer, T.; Meinert, R.; Studnicka-Benke, A.; Hajek, K.; Spengler, J. D.; Neumann, M. G. (1995) Acidic particles and lung function in children: a summer camp study in the Austrian Alps. Am. J. Respir. Crit. Care Med. 151: 423-430.

Styer, P.; McMillan, N.; Gao, F.; Davis, J.; Sacks, J. (1995) The effect of airborne particulate matter on daily death counts. Environ. Health Perspect. 103: 490-497.

Suh, H. H.; Koutrakis, P.; Spengler, J. D. (1993) Validation of personal exposure models for sulfate and aerosol strong acidity. J. Air Waste Manage. Assoc. 43: 845-850.

Svartengren, K.; Lindestad, P.-Å.; Svartengren, M.; Bylin, G.; Philipson, K.; Camner, P. (1994) Deposition of inhaled particles in the mouth and throat of asthmatic subjects. Eur. Respir. J. 1467-1473.

Takenaka, S.; Dornhöfer-Takenaka, H.; Muhle, H. (1986) Alveolar distribution of fly ash and of titanium dioxide after long-term inhalation by Wistar rats. J. Aerosol Sci. 17: 361-364.

Targonski, P. V.; Persky, V. W.; Ramekrishnan, V. (1995) Effect of environmental molds on risk of death from asthma during the pollen season. J. Allergy Clin. Immunol. 95: 955-961.

Thatcher, T. L.; Layton, D. W. (1995) Deposition, resuspension, and penetration of particles within a residence. Atmos. Environ. 29: 1487-1497.

Thurston, G. D.; Kinney, P. L. (1995) Air pollution epidemiology: considerations in time-series modeling. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity; January 1994; Irvine, CA. Inhalation Toxicol. 7: 71-83.

Thurston, G. D.; Ito, K.; Lippmann, M.; Hayes, C. (1989) Reexamination of London, England, mortality in relation to exposure to acidic aerosols during 1963-1972 winters. In: Symposium on the health effects of acid aerosols; October 1987; Research Triangle Park, NC. Environ. Health Perspect. 79: 73-82.

Thurston, G. D.; Ito, K.; Kinney, P. L.; Lippmann, M. (1992) A multi-year study of air pollution and respiratory hospital admissions in three New York State metropolitan areas: results for 1988 and 1989 summers. J. Exposure Anal. Environ. Epidemiol. 2: 429-450.

Thurston, G. D.; Ito, K.; Hayes, C. G.; Bates, D. V.; Lippmann, M. (1994) Respiratory hospital admissions and summertime haze air pollution in Toronto, Ontario: consideration of the role of acid aerosols. Environ. Res. 65: 271-290.

Touloumi, G.; Pocock, S. J.; Katsouyanni, K.; Trichopoulos, D. (1994) Short-term effects of air pollution on daily mortality in Athens: a time-series analysis. Int. J. Epidemiol. 23: 957-967.

U.S. Bureau of the Census. (1992) Statistical abstract of the United States 1992. 112th ed. Washington, DC: U.S. Department of Commerce.

U.S. Environmental Protection Agency. (1982) Air quality criteria for particulate matter and sulfur oxides. Research Triangle Park, NC: Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office; EPA report no. EPA-600/8-82-029aF-cF. 3v. Available from: NTIS, Springfield, VA; PB84-156777.

Utell, M. J.; Frampton, M. W. (1995) Particles and mortality: a clinical perspective. In: Phalen, R. F.; Bates, D. V., eds. Proceedings of the colloquium on particulate air pollution and human mortality and morbidity, part II; January 1994; Irvine, CA. Inhalation Toxicol. 7: 645-655.

Vincent, J. H. (1995) Standards for health-related aerosol measurement and control. In: Aerosol science for industrial hygienists; Oxford, United Kingdom: Pergamon; pp. 204-237.

Ware, J. H.; Ferris, B. G., Jr.; Dockery, D. W.; Spengler, J. D.; Stram, D. O.; Speizer, F. E. (1986) Effects of ambient sulfur oxides and suspended particles on respiratory health of preadolescent children. Am. Rev. Respir. Dis. 133: 834-842.

Warheit, D. B.; Seidel, W. C.; Carakostas, M. C.; Hartsky, M. A. (1990) Attenuation of perfluoropolymer fume pulmonary toxicity: effect of filters, combustion method, and aerosol age. Exp. Mol. Pathol. 52: 309-329.

Weiss, K. B.; Wagener, D. K. (1990) Changing patterns of asthma mortality: identifying target populations at high risk. JAMA J. Am. Med. Assoc. 264: 1683-1687.

Whitby, K. T. (1978) The physical characteristics of sulfur aerosols. Atmos. Environ. 12: 135-159.

White, M. C.; Etzel, R. A.; Wilcox, W. D.; Lloyd, C. (1994) Exacerbations of childhood asthma and ozone pollution in Atlanta. Environ. Res. 65: 56-68.

Widdicombe, J.; Sant'Ambrogio, G.; Mathew, O. P. (1988) Nerve receptors of the upper airway. In: Mathew, O. P.; Sant'Ambrogio, G., eds. Respiratory function of the upper airway. New York, NY: Marcel Dekker; pp. 193-231. (Lung biology in health and disease: v. 35).

Wilson, W. E.; Suh, H. H. (1996) Fine and coarse particles: concentration relationships relevant to epidemiological studies. J. Air Waste Manage. Assoc.: accepted.

Wilson, W. E.; Spiller, L. L.; Ellestad, T. G.; Lamothe, P. J.; Dzubay, T. G.; Stevens, R. K.; Macias, E. S.; Fletcher, R. A.; Husar, J. D.; Husar, R. B.; Whitby, K. T.; Kittelson, D. B.; Cantrell, B. K. (1977) General Motors sulfate dispersion experiment: summary of EPA measurements. J. Air Pollut. Control Assoc. 27: 46-51.

Wyzga, R. E.; Lipfert, F. W. (1995) Temperature-pollution interactions with daily mortality in Philadelphia. In: Particulate matter: health and regulatory issues: proceedings of an international specialty conference; April; Pittsburgh, PA. Pittsburgh, PA: Air & Waste Management Association; pp. 3-42. (A&WMA publication VIP-49).

APPENDIX 13A

REFERENCES USED TO DERIVE CELL RATINGS IN TEXT TABLES 13-6 AND 13-7 FOR ASSESSING QUALITATIVE STRENGTH OF EVIDENCE FOR PM-RELATED HEALTH EFFECTS

TABLE 13A-1 (ANALOG OF TABLE 13-6). QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON SHORT-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS

		Health Measure and PM Indicator															
		Mortality				Hospitalization and Outpatient Visits				Community-Based Morbidity/Symptoms				Changes in Lung Function			
Population Group	Subgroup	ThP	FP	CP	$SO_4^=$ or Acid	ThP	FP	CP	$SO_4^=$ or Acid	ThP	FP	CP	$SO_4^=$ or Acid	ThP	FP	CP	$SO_4^=$ or Acid
Adults	General Population	1 +++	2 ++	3 +/-*	4 +	17 +	18 0	19 ID**	20 0	33 +/-	34 0	35 0	36 +/-	49 +	50 0	51 0	52 0
	Elderly	5 +	6 +	7 0	8 0	21 ++	22 0	23 0	24 0	37 0	38 0	39 0	40 0	53 0	54 0	55 0	56 0
	Respiratory	9 ++	10 +	11 0	12 0	25 ++	26 +/-	27 ID	28 ++	41 +✓	42 +✓	43 0	44 +✓	57 0	58 0	59 0	60 0
	Cardiovascular	13 +	14 +	15 0	16 0	29 +	30 0	31 0	32 +	45 0	46 0	47 0	48 0	61 0	62 0	63 0	64 0
Children	General Population	65 ID	66 0	67 0	68 0	73 +	74 0	75 ID**	76 +/-	81 +	82 +	83 0	84 +/-	89 ++	90 +	91 0	92 +
	Pre-existing Respiratory Conditions	69 0	70 0	71 0	72 0	77 0	78 0	79 0	80 0	85 +	86 +/-	87 0	88 +/-	93 +	94 ID	95 0	96 +/-
Asthmatics	Regardless of Age	97 0	98 0	99 0	100 0	101 ++	102 +/-	103 +/-**	104 +	105 +	106 +/-	107 ID	108 +/-	109 +	110 +/-	111 ID	112 +/-

ThP = Index of thoracic particles, usually measured PM_{10} or PM_{15}.
FP = Index of fine-mode fraction of thoracic particles, usually measured $PM_{2.5}$ or $PM_{2.1}$.
CP = Index of coarse-mode fraction of thoracic particles, usually the calculated or measured difference between PM_{10} or PM_{15} and $PM_{2.5}$ or $PM_{2.1}$.
Cells 1, 2, 3, 4: Effect of specified indicator on total mortality or total non-accidental mortality, regardless of age.
Cells 5, 6, 7, 8: Generally, effect of specified indicator on mortality in persons at least 65 years old.
Cells 9, 10, 11, 12: Effect of specified indicator on respiratory causes of death.
Cells 13, 14, 15, 16: Effect of specified indicator on cardiovascular causes of death.
Cells 17 to 64: Effect of specified indicator on total hospital admissions or outpatient visits, respiratory symptoms or changes in lung function in adults.
Cells 69-72, 77-80, 85-88, 93-96: Effect of specified indicator in children with history of pre-existing respiratory illness or symptoms, excluding asthma.
Cells 97 to 112: Mortality or exacerbation of existing asthma (not increased incidence of new asthma) among asthmatic individuals, regardless of age.
0 = No pertinent studies identified.
ID = Insufficient data: at least 1 pertinent study identified but inference as to weight of evidence not warranted.
+/- = Few pertinent studies identified, weight of evidence uncertain but somewhat positive.
+ to +++ = Increasingly stronger, more consistent positive evidence.
*Based on significant positive association for mortality in Steubenville with CP found by Schwartz et al. (1996); but CP highly correlated with FP.
**CP not measured directly in Gordian et al. (1996) and/or Hefflin et al. (1994), but PM_{10} measured in CP-dominated polluted air.
✓ThP designation based on BS in London having D_{50} cutpoint = 4.5 μm that includes some ThP particles, but probably more closely indexes FP as also designated along with acid actually measured as H_2SO_4 in Lawther et al. (1970) study.

TABLE 13A-2. REFERENCES USED IN RATING CELLS OF MAIN TEXT TABLE 13-6 (AND TABLE 13A-1): QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON SHORT-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS[1]

THORACIC PM	FINE PM	COARSE PM	SULFATES OR ACID
ADULTS: MORTALITY			
CELL 1 (+++) Dockery et al., 1992 Ito et al., 1995 Kinney et al., 1995 Lyon et al., 1995 Ostro et al., 1996 Pope et al., 1992 Pope and Kalkstein, 1996 Schwartz, 1993 Schwartz et al., 1996a Styer et al., 1995	CELL 2 (++) Dockery et al., 1992 Schwartz et al., 1996a	CELL 3 (+/-) Schwartz et al., 1996a	CELL 4 (+) Dockery et al., 1992 Ito et al., 1993 Lippmann and Ito, 1995 Schwartz et al., 1996a Thurston et al., 1989
CELL 5 (+) Lyon et al., 1995 Ostro et al., 1996 Saldiva et al., 1995 Styer et al, 1995	CELL 6 (+) Schwartz et al., 1996a	CELL 7 (0) No pertinent studies identified.	CELL 8 (0) No pertinent studies identified.
CELL 9 (++) Ostro et al., 1996 Pope et al., 1992 Pope and Kalkstein, 1996	CELL 10 (+) Schwartz et al., 1996a	CELL 11 (0) No pertinent studies identified.	CELL 12 (0) No pertinent studies identified.
CELL 13 (+) Pope et al, 1992 Pope and Kalkstein, 1996	CELL 14 (+) Schwartz et al., 1996a	CELL 15 (0) No pertinent studies identified.	CELL 16 (0) No pertinent studies identified.
ADULTS: HOSPITALIZATION AND OUTPATIENT VISITS			
CELL 17 (+) Gordian et al., 1996 Hefflin et al., 1994	CELL 18 (0) No pertinent studies identified.	CELL 19 (+/-) Gordian et al., 1996 Hefflin et al., 1994	CELL 20 (0) No pertinent studies identified.

TABLE 13A-2 (cont'd). REFERENCES USED IN RATING CELLS OF MAIN TEXT TABLE 13-6 (AND TABLE 13A-1): QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON SHORT-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS[1]

THORACIC PM	FINE PM	COARSE PM	SULFATES OR ACID
ADULTS: HOSPITALIZATION AND OUTPATIENT VISITS			
CELL 21 (++) Schwartz, 1994d Schwartz, 1994e Schwartz, 1994f Schwartz, 1995 Schwartz, 1996 Schwartz and Morris, 1995 Schwartz et al., 1996b	CELL 22 (0) No pertinent studies identified.	CELL 23 (0) No pertinent studies identified.	CELL 24 (0) No pertinent studies identified.
ADULTS: HOSPITALIZATION AND OUTPATIENT VISITS, CONT.			
CELL 25 (++) Lamm et al., 1994 Pope, 1989 Pope, 1991 Schwartz, 1994d,e,f Schwartz, 1995 Schwartz, 1996 Schwartz et al., 1996b Thurston et al., 1994	CELL 26 (+/-) Thurston et al., 1994	CELL 27 (ID) Thurston et al., 1994	CELL 28 (++) Bates and Sizto, 1987 Bates and Sizto, 1989 Burnett et al., 1994 Burnett et al., 1995 Delfino et al., 1994 Thurston et al., 1992 Thurston et al., 1994
CELL 29 (+) Schwartz and Morris, 1995	CELL 30 (0) No pertinent studies identified.	CELL 31 (0) No pertinent studies identified.	CELL 32 (+) Burnett et al., 1995
ADULTS: COMMUNITY-BASED MORBIDITY AND SYMPTOMS			
CELL 33 (+/-) Dusseldorp et al., 1994	CELL 34 (0) No pertinent studies identified.	CELL 35 (0) No pertinent studies identified.	CELL 36 (+/-) Ostro et al., 1993
CELL 37 (0) No pertinent studies identified.	CELL 38 (0) No pertinent studies identified.	CELL 39 (0) No pertinent studies identified.	CELL 40 (0) No pertinent studies identified.
CELL 41 (+) Lawther et al., 1970	CELL 42 (+) Lawther et al., 1970	CELL 43 (0) No pertinent studies identified.	CELL 44 (+) Lawther et al., 1970

TABLE 13A-2 (cont'd). REFERENCES USED IN RATING CELLS OF MAIN TEXT TABLE 13-6 (AND TABLE 13A-1): QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON SHORT-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS[1]

THORACIC PM	FINE PM	COARSE PM	SULFATES OR ACID
ADULTS: COMMUNITY-BASED MORBIDITY AND SYMPTOMS			
CELL 45 (0) No pertinent studies identified.	CELL 46 (0) No pertinent studies identified.	CELL 47 (0) No pertinent studies identified.	CELL 48 (0) No pertinent studies identified.
ADULTS: CHANGES IN LUNG FUNCTION			
CELL 49 (+) Dusseldorp et al., 1994 Pope and Kanner, 1993	CELL 50 (0) No pertinent studies identified.	CELL 51 (0) No pertinent studies identified.	CELL 52 (0) No pertinent studies identified.
CELL 53 (0) No pertinent studies identified.	CELL 54 (0) No pertinent studies identified.	CELL 55 (0) No pertinent studies identified.	CELL 56 (0) No pertinent studies identified.
CELL 57 (0) No pertinent studies identified.	CELL 58 (0) No pertinent studies identified.	CELL 59 (0) No pertinent studies identified.	CELL 60 (0) No pertinent studies identified.
CELL 61 (0) No pertinent studies identified.	CELL 62 (0) No pertinent studies identified.	CELL 63 (0) No pertinent studies identified.	CELL 64 (0) No pertinent studies identified.
CHILDREN: MORTALITY			
CELL 65 (ID) Lyon et al., 1995 Saldiva et al., 1994	CELL 66 (0) No pertinent studies identified.	CELL 67 (0) No pertinent studies identified.	CELL 68 (0) No pertinent studies identified.
CELL 69 (0) No pertinent studies identified.	CELL 70 (0) No pertinent studies identified.	CELL 71 (0) No pertinent studies identified.	CELL 72 (0) No pertinent studies identified.
CHILDREN: HOSPITALIZATION AND OUTPATIENT VISITS			
CELL 73 (+) Gordian et al., 1996 Hefflin et al., 1994 Lamm et al., 1994 Pope, 1989 Pope, 1991	CELL 74 (0) No pertinent studies identified.	CELL 75 (+/-) Gordian et al., 1996 Hefflin et al., 1994	CELL 76 (+/-) Burnett et al., 1994

TABLE 13A-2 (cont'd). REFERENCES USED IN RATING CELLS OF MAIN TEXT TABLE 13-6 (AND TABLE 13A-1): QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON SHORT-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS[1]

THORACIC PM	FINE PM	COARSE PM	SULFATES OR ACID
CHILDREN: HOSPITALIZATION AND OUTPATIENT VISITS			
CELL 77 (0) No pertinent studies identified.	CELL 78 (0) No pertinent studies identified.	CELL 79 (0) No pertinent studies identified.	CELL 80 (0) No pertinent studies identified.
CHILDREN: COMMUNITY-BASED MORBIDITY AND SYMPTOMS			
CELL 81 (+) Hoek and Brunekreef,1993,1994,1995 Pope and Dockery, 1992 Pope et al., 1991 Schwartz et al., 1994	CELL 82 (+) Neas et al, 1995 Schwartz et al., 1994	CELL 83 (0) No pertinent studies identified.	CELL 84 (+/-) Hoek and Brunekreef, 1994, 1995 Neas et al., 1995 Schwartz et al., 1994
CELL 85 (+) Pope and Dockery, 1992 Roemer et al., 1993	CELL 86 (+/-) Neas et al., 1995	CELL 87 (0) No pertinent studies identified.	CELL 88 (+/-) Neas et al., 1995
CHILDREN: CHANGES IN LUNG FUNCTION			
CELL 89 (++) Hoek and Brunekreef, 1993, 1994 Johnson et al., 1990 Neas et al., 1995 Pope and Dockery, 1992 Pope et al., 1991 Spektor et al., 1988 Studnicka et al., 1995	CELL 90 (+) Dassen et al., 1986 Johnson et al., 1990 Koenig et al., 1993 Neas et al., 1995	CELL 91 (0) No pertinent studies identified.	CELL 92 (+) Bock et al., 1985 Hoek and Brunekreef, 1994 Neas et al., 1995 Raizenne et al., 1989 Spektor et al., 1988 Studnicka et al., 1995
CELL 93 (+) Neas et al., 1995 Pope and Dockery, 1992 Roemer et al., 1993	CELL 94 (ID) Neas et al., 1995	CELL 95 (0) No pertinent studies identified.	CELL 96 (+/-) Neas et al., 1995
ASTHMATICS: MORTALITY			
CELL 97 (0) No pertinent studies identified.	CELL 98 (0) No pertinent studies identified.	CELL 99 (0) No pertinent studies identified.	CELL 100 (0) No pertinent studies identified.

TABLE 13A-2 (cont'd). REFERENCES USED IN RATING CELLS OF MAIN TEXT TABLE 13-6 (AND TABLE 13A-1): QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON SHORT-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS[1]

THORACIC PM	FINE PM	COARSE PM	SULFATES OR ACID
ASTHMATICS: HOSPITALIZATION AND OUTPATIENT VISITS			
CELL 101 (++) Delfino et al., 1994 Gordian et al., 1996 Pope, 1989 Pope, 1991 Schwartz, 1994d Schwartz et al., 1993 Thurston et al., 1994 White et al., 1994	CELL 102 (+/-) Thurston et al., 1994	CELL 103 (+/-) Gordian et al., 1996 Thurston et al., 1994	CELL 104 (+) Bates and Sizto, 1987 Thurston et al., 1992 Thurston et al., 1994
ASTHMATICS: COMMUNITY-BASED MORBIDITY/SYMPTOMS			
CELL 105 (+) Ostro et al., 1995 Pope et al., 1991 Roemer et al., 1993	CELL 106 (+/-) Ostro et al., 1991 Perry et al., 1983	CELL 107 (ID) Perry et al., 1983	CELL 108 (+/-) Ostro et al., 1991 Perry et al., 1983
ASTHMATICS: CHANGES IN LUNG FUNCTION			
CELL 109 (+) Pope et al., 1991 Roemer et al., 1993 Silverman et al., 1992 Studnicka et al., 1995	CELL 110 (+/-) Koenig et al., 1993 Perry et al., 1983	CELL 111 (ID) Perry et al., 1983	CELL 112 (+/-) Perry et al., 1983 Raizenne et al., 1989 Studnicka et al., 1995

[1]References are cited as in the reference list of Chapter 13.

TABLE 13A-3 (ANALOG OF TABLE 13-7). QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON LONG-TERM EXPOSURE TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS

		Health Measure and PM Indicator											
		Mortality				Community-Based Morbidity/ Symptoms				Changes in Lung Function			
Population Group	Subgroup	ThP	FP	CP	$SO_4^=$ or Acid	ThP	FP	CP	$SO_4^=$ or Acid	ThP	FP	CP	$SO_4^=$ or Acid
Adults	General Population	1 ++	2 ++	3 +/-*	4 ++	13 +/-	14 +/-	15 0	16 +	25 +/-	26 0	27 0	28 ID
	Elderly	5 0	6 0	7 0	8 0	17 0	18 0	19 0	20 0	29 0	30 0	31 0	32 0
	Cardiopulmonary	9 ++	10 +++	11 0	12 ++	21 0	22 0	23 0	24 0	33 0	34 0	35 0	36 0
Children	General Population	37 +/-	38 0	39 0	40 0	41 +	42 +	43 0	44 ++	45 +/-	46 ID	47 0	48 +
Asthmatics	Regardless of Age	49 0	50 0	51 0	52 0	53 +	54 +/-	55 0	56 +/-	57 0	58 0	59 0	60 0

ThP = Index of thoracic particles, usually measured PM_{10} or PM_{15}.
FP = Index of fine-mode fraction of thoracic particles, usually measured $PM_{2.5}$ or $PM_{2.1}$.
CP = Index of coarse-mode fraction of thoracic particles, usually the calculated or measured difference between PM_{10} or PM_{15} and $PM_{2.5}$ or $PM_{2.1}$.
Cells 1, 2, 3, 4: Effect of specified indicator on total mortality or mortality due to natural causes, regardless of age.
Cells 9 to 12: Effect of specified indicator on combined cardiovascular and non-malignant respiratory causes of death.
Cell 37: Only infant mortality studied.
Cells 49 to 60: Mortality, exacerbation of existing asthma, increased incidence of new asthma, or lung function changes in asthmatics regardless of age.
0 = No pertinent studies identified.
ID = Insufficient data: at least 1 pertinent study identified but inference as to weight of evidence not warranted.
+/- = Few pertinent studies identified, weight of evidence uncertain, but somewhat positive.
+ to +++ = Increasingly stronger, more consistent positive evidence.
*Based on supplemental reanalysis by U.S. EPA of results from Dockery et al. (1993), see Figure 12-8 in Chapter 12.

TABLE 13A-4. REFERENCES USED IN RATING CELLS OF TABLE 13-7 (AND TABLE 13A-3)
QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON LONG-TERM EXPOSURE
TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS[1]

THORACIC PM	FINE PM	COARSE PM	SULFATES OR ACID
ADULTS: MORTALITY			
CELL 1 (++) Dockery et al., 1993 Lipfert et al., 1988 Lipfert, 1993 Ozkaynak and Thurston, 1987	CELL 2 (++) Dockery et al., 1993 Lipfert et al., 1988 Lipfert, 1993 Ozkaynak and Thurston, 1987 Pope et al., 1995	CELL 3 (+/-) Supplemental EPA analysis of Dockery et al., 1993 (see Chapter 12, Figure 12-8).	CELL 4 (++) Dockery et al., 1993 Lipfert et al., 1988 Lipfert, 1993 Ozkaynak and Thurston, 1987 Pope et al, 1995
CELL 5 (0) No pertinent studies identified.	CELL 6 (0) No pertinent studies identified.	CELL 7 (0) No pertinent studies identified.	CELL 8 (0) No pertinent studies identified.
CELL 9 (++) Dockery et al., 1993	CELL 10 (+++) Dockery et al., 1993 Pope et al., 1995	CELL 11 (0) No pertinent studies identified.	CELL 12 (++) Dockery et al., 1993 Lipfert, 1993 Pope et al., 1995
ADULTS: COMMUNITY-BASED MORBIDITY AND SYMPTOMS			
CELL 13 (+/-) Abbey et al., 1995a Abbey et al., 1995b	CELL 14 (+/-) Abbey et al., 1995a Abbey et al., 1995b	CELL 15 (0) No pertinent studies identified.	CELL 16 (+) Abbey et al., 1995a Abbey et al., 1995b Chapman et al., 1985
CELL 17 (0) No pertinent studies identified.	CELL 18 (0) No pertinent studies identified.	CELL 19 (0) No pertinent studies identified.	CELL 20 (0) No pertinent studies identified.
CELL 21 (0) No pertinent studies identified.	CELL 22 (0) No pertinent studies identified.	CELL 23 (0) No pertinent studies identified.	CELL 24 (0) No pertinent studies identified.
ADULTS: CHANGES IN LUNG FUNCTION			
CELL 25 (+/-) Ackermann-Liebrich et al., 1996	CELL 26 (0) No pertinent studies identified.	CELL 27 (0) No pertinent studies identified.	CELL 28 (ID) Jedrychowski and Krzyzanowski, 1989
CELL 29 (0) No pertinent studies identified.	CELL 30 (0) No pertinent studies identified.	CELL 31 (0) No pertinent studies identified.	CELL 32 (0) No pertinent studies identified.
CELL 33 (0) No pertinent studies identified.	CELL 34 (0) No pertinent studies identified.	CELL 35 (0) No pertinent studies identified.	CELL 36 (0) No pertinent studies identified.

TABLE 13A-4 (cont'd). REFERENCES USED IN RATING CELLS OF TABLE 13-7 (AND TABLE 13A-3)
QUALITATIVE SUMMARY OF COMMUNITY EPIDEMIOLOGIC FINDINGS ON LONG-TERM EXPOSURE
TO AMBIENT THORACIC PARTICLES AND SELECTED CONSTITUENTS[1]

THORACIC PM	FINE PM	COARSE PM	SULFATES OR ACID
CHILDREN: MORTALITY			
CELL 37 (+/-) Bobak and Leon, 1992	CELL 38 (0) No pertinent studies identified.	CELL 39 (0) No pertinent studies identified.	CELL 40 (0) No pertinent studies identified.
CHILDREN: COMMUNITY-BASED MORBIDITY AND SYMPTOMS			
CELL 41 (+) Dockery et al., 1989 Dockery et al., 1996 Speizer, 1989	CELL 42 (+) Dockery et al., 1989 Dockery et al., 1996 Speizer, 1989	CELL 43 (0) No pertinent studies identified.	CELL 44 (++) Dockery et al., 1989, 1996 Dodge et al., 1985 Speizer, 1989 Stern et al., 1989, 1994 Ware et al., 1986
CHILDREN: CHANGES IN LUNG FUNCTION			
CELL 45 (+/-) Dockery et al., 1989 Johnson et al., 1990 Raizenne et al., 1996 Spektor et al., 1991	CELL 46 (ID) Dockery et al., 1989 Johnson et al., 1990 Raizenne et al., 1996	CELL 47 (0) No pertinent studies identified.	CELL 48 (+) Dockery et al., 1989 Raizenne et al., 1996 Stern et al., 1989, 1994
ASTHMATICS: MORTALITY			
CELL 49 (0) No pertinent studies identified.	CELL 50 (0) No pertinent studies identified.	CELL 51 (0) No pertinent studies identified.	CELL 52 (0) No pertinent studies identified.
ASTHMATICS: COMMUNITY-BASED MORBIDITY/SYMPTOMS			
CELL 53 (+) Abbey et al., 1995a, 1995b Dockery et al., 1989	CELL 54 (+/-) Abbey et al., 1995a Abbey et al., 1995b	CELL 55 (0) No pertinent studies identified.	CELL 56 (+/-) Abbey et al., 1995a Abbey et al., 1995b
ASTHMATICS: CHANGES IN LUNG FUNCTION			
CELL 57 (0) No pertinent studies identified.	CELL 58 (0) No pertinent studies identified.	CELL 59 (0) No pertinent studies identified.	CELL 60 (0) No pertinent studies identified.