Research Priorities for Airborne Particulate Matter: IV. Continuing Research Progress

Committee on Research Priorities for Airborne Particulate Matter, National Research Council

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Research Priorities for Airborne Particulate Matter

•IV•

Continuing Research Progress

Committee on Research Priorities for
Airborne Particulate Matter

Board on Environmental Studies and Toxicology

Division on Earth and Life Studies

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Dedication to the Memory of Professor Glen Cass (1947-2001)

We dedicate this report to the memory of our late colleague and fellow committee member, Professor Glen Cass. Glen represented superbly the multidisciplinary research approach that we advocate in this report. Over the past two decades, from his Ph.D. research on sulfates to subsequent work on ozone, nitrates, primary and secondary carbon, visibility reduction, and indoor air quality, Glen and his research group unraveled the sources, atmospheric processes, toxicity, and emission controls needed to curtail the detrimental impacts of particulate matter on public health and welfare. Glen had a unique ability to combine elegant scientific approaches with sound engineering judgment to arrive at practical solutions that have been incorporated into air quality management practices in Los Angeles, the northeastern United States, and Asia. His legacy includes a large body of research and a rigorous, yet practical, approach to training a generation of air pollution scientists, who continue to lay the foundation needed for science-based decisionmaking. As a colleague, a friend, and an inspiration, we all sorely miss him.

Preface

Under the Clean Air Act, particulate matter (PM) is one of the major air pollutants for which National Ambient Air Quality Standards (NAAQS) are to be established on the basis of the scientific evidence on risks to human health. The U.S. Environmental Protection Agency (EPA), other federal and state government agencies, and nongovernment organizations are conducting a major multiyear research effort to improve scientific understanding of airborne PM and its effects on human health. An overall objective is to reduce uncertainties in the scientific evidence used to set the NAAQS for airborne PM in the United States. At the request of Congress and EPA, the National Research Council's Committee on Research Priorities for Airborne Particulate Matter was established in 1998 and given the charge of developing a research agenda for this purpose and then monitoring research progress. Biosketches of the committee members are presented in Appendix A. This report, the committee's fourth, comes 6 years after its first report, which proposed a 13-year research portfolio. This report evaluates research progress since the first report, evaluates possible barriers to continued progress, and makes recommendations for future research directions and research management.

The first of the committee's four planned reports, *Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio*, was published in 1998. It identified 10 high-priority research topics linked to key policy-related scientific uncertainties and presented a 13-year "research investment portfolio" containing recommended short-term and long-term phasing and estimated costs of research on each topic. Congress, EPA, and the scientific community gave strong support to the committee's recommendations and implemented substantial changes in research efforts in response to them.

The committee's second report, *Research Priorities for Airborne Particulate Matter: II. Evaluating Research Progress and Updating the Portfolio,* published in 1999, described the committee's plans for monitoring the progress of research. In addition, the research recommendations from the committee's first report were updated, and recommendations related to emissions and air quality models were substantially revised.

The committee's third report, published in 2001, monitored the prog-

ress of the research begun in 1998 or later to address the priority research topics identified by the committee. Although much research had been initiated, not enough time had elapsed by then for many of the projects to be completed and their results reported. The third report should be viewed as a preliminary assessment of research progress.

In this final report, the committee faced the challenge of gauging research progress on each of its 10 research topics. It developed an approach for characterizing the degree to which new evidence has reduced uncertainty and then gathered and evaluated the evidence coming from research over 5 years since the first report. The committee was assisted by the many individuals (listed below) who participated in workshops and public sessions of committee meetings held for the purpose of learning about relevant findings. Research progress reflects not only the creativity and efforts of researchers but also the efficiency of research management. This report also provides recommendations for future consideration of research on PM, as this committee's work is now finished.

The committee received oral or written presentations or both from the following individuals:

John Bachmann, U.S. Environmental Protection Agency; Tina Bahadori, American Chemistry Council; John Bailar, University of Chicago; David V. Bates, University of British Columbia; William Bennett, University of North Carolina at Chapel Hill; Michael Brauer, University of British Columbia; Richard Burnett, Health Canada; Lilian Calderon-Garciduenas, University of North Carolina at Chapel Hill; Aaron Cohen, Health Effects Institute; Daniel Costa, U.S. Environmental Protection Agency; Robin Dennis, U.S. Environmental Protection Agency; Robert Devlin, U.S. Environmental Protection Agency; Douglas Dockery, Harvard School of Public Health; Francesca Dominici, Johns Hopkins Bloomberg School of Public Health; Ed Edney, U.S. Environmental Protection Agency; Mark Frampton, University of Rochester; John Froines, University of California at Los Angeles; Patrick Gaffney, California Air Resources Board; Chris Geron, U.S. Environmental Protection Agency; Frank Gilliland, University of Southern California; Ian Gilmour, U.S. Environmental Protection Agency; John Godleski, Harvard School of Public Health; Judy Graham, while at the U.S. Environmental Protection Agency, currently at the American Chemistry Council; Jack Harkema, Michigan State University; Bruce Harris, U.S. Environmental Protection Agency; James Hogg, University of British Columbia; Patrick Kinney, Columbia University School of Public Health; Michael Kleinman, University of California at Irvine; Jane Koenig, University of Washington; Timothy Larson, University of Washington; Allen Lefohn, A.S.L. & Associates; Chuck Lewis, U.S. Environ-

mental Protection Agency; Joellen Lewtas, U.S. Environmental Protection Agency; Morton Lippmann, New York University School of Medicine; Phillip Lorang, U.S. Environmental Protection Agency; Robert Mason, National Jewish Medical and Research Center; Andrew Miller, U.S. Environmental Protection Agency; Fred Miller, CIIT Centers for Health Research; David Mobley, U.S. Environmental Protection Agency; D. Warner North, NorthWorks; William Ollison, American Petroleum Institute; Wayne Ott, Stanford University; Pedro Oyola, Chilean National Commission for the Environment; Joseph Paisie, U.S. Environmental Protection Agency; Giovanni Parmigiani, Johns Hopkins University; Robert Phalen, University of California at Irvine; C. Arden Pope III, Brigham Young University; Peter Preuss, U.S. Environmental Protection Agency; Charles Rodes, Research Triangle Institute; Joseph Rodricks, ENVIRON International Corporation; Armistead Russell, Georgia Institute of Technology; Richard Scheffe, U.S. Environmental Protection Agency; Kenneth Schere, U.S. Environmental Protection Agency; John Seitz, while at the U.S. Environmental Protection Agency, currently at Sonnenschein, Nath & Rosenthal, LLP; Linda Sheldon, U.S. Environmental Protection Agency; Lianne Sheppard, University of Washington; Dean Smith, U.S. Environmental Protection Agency; Paul Solomon, U.S. Environmental Protection Agency; Helen Suh, Harvard School of Public Health; Joseph Tikvart, U.S. Environmental Protection Agency; Paige Tolbert, Emory University; Sverre Vedal, National Jewish Medical and Research Center; James Vickery, U.S. Environmental Protection Agency; Russell Weiner, U.S. Environmental Protection Agency; Ronald Williams, U.S. Environmental Protection Agency; William Wilson, U.S. Environmental Protection Agency; and Denis Zmirou, French Institute of Health and Medical Research.

We are grateful for the assistance of the NRC staff in preparing the report. We wish to thank Raymond Wassel, project director, and James Reisa, director of BEST. Scientific and technical information was provided by Eileen Abt, Kulbir Bakshi, K. John Holmes, Karl Gustavson, Amanda Staudt, Mirsada Karalic-Loncarevic, and Rachel Hoffman. Invaluable logistical support was provided by Emily Brady. The report was ably edited by Ruth Crossgrove.

Finally, I would like to thank all the members of the committee for their dedicated efforts throughout the development of this report.

Jonathan Samet, Chair
Committee on Research Priorities for
Airborne Particulate Matter

Acknowledgment of Review Participants

This report has been reviewed in draft form by individuals chosen for their diverse perspectives and technical expertise, in accordance with procedures approved by the National Research Council's Report Review Committee. The purpose of this independent review is to provide candid and critical comments that will assist the institution in making its published report as sound as possible and to ensure that the report meets institutional standards for objectivity, evidence, and responsiveness to the study charge. The review comments and draft manuscript remain confidential to protect the integrity of the deliberative process. We wish to thank the following individuals for their review of this report:

Carol Henry, American Chemistry Council; George Hidy, ENVAIR; Morton Lippmann, New York University Medical Center; Ronald Low, University of Medicine and Dentistry of New Jersey; D. Warner North, NorthWorks; Robert Phalen, University of California at Irvine; C. Arden Pope, Brigham Young University; and Armistead Russell, Georgia Institute of Technology.

Although the reviewers listed above have provided many constructive comments and suggestions, they were not asked to endorse the conclusions or recommendations, nor did they see the final draft of the report before its release. The review of this report was overseen by Annetta Watson, Oak Ridge National Laboratory. Appointed by the NRC she was responsible for making certain that an independent examination of this report was carried out in accordance with institutional procedures and that all review comments were carefully considered. Responsibility for the final content of this report rests entirely with the authoring committee and the institution.

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Research Priorities for Airborne Particulate Matter: IV. Continuing Research Progress

Summary

This report is the fourth in a series by the Committee on Research Priorities for Airborne Particulate Matter. The committee was convened by the National Research Council (NRC) in January 1998 at the request of the U.S. Environmental Protection Agency (EPA) following directions from Congress in EPA's fiscal year 1998 appropriations report. The congressional request for this study arose from the need to reduce uncertainties in the scientific evidence considered by EPA in reaching the July 1997 decision to establish new National Ambient Air Quality Standards (NAAQS) for particulate matter (PM) less than 2.5 micrometers (μm) in aerodynamic diameter ($PM_{2.5}$). Anticipating information needs of the required reviews of the PM NAAQS every 5 years, Congress appropriated substantial funds for a major research program to reduce the scientific uncertainties. It also directed EPA to arrange for this independent NRC study to provide guidance for planning the research program and then monitoring research progress. This report focuses on the progress since early 1998 in reducing scientific uncertainties.

THE PARTICULATE MATTER RESEARCH PROGRAM

EPA initiated a substantial program that largely followed the 13-year research portfolio set out over 5 years ago by this committee in its first report. The portfolio identifies 10 high-priority research topics linked to key scientific uncertainties relevant to those sources that cause adverse health effects (see Box S-1). Table S-1 shows funding levels budgeted during fiscal years 1998-2003 by Congress for EPA's PM research and related technical work. Much of the research called for by the committee has been carried out by EPA investigators, but many scientists from academia and

research institutes in the United States and in other countries are also involved.

REVIEW OF PROGRESS AND STATUS OF RESEARCH

In preparing this final report, the committee matched PM research and resulting contributions to the scientific literature from projects sponsored by EPA and other institutions against the committee's recommended research portfolio. It assessed the extent to which completed and ongoing research is addressing gaps in the evidence on major issues that decision-makers will consider as they review the scientific evidence relevant to the PM NAAQS. The committee systematically reviewed progress made between 1998 and mid-2002 in PM research on its topics 1-10. Review updates were performed over the next year as this report was written. Brief summaries for each topic follow.

Research Topic 1. Outdoor Measures Versus Actual Human Exposures

Substantial progress has been made in addressing topic 1, in part because of leadership by EPA in this area. The committee was able to identify a large number of studies initiated after its first report, and for most, the field work is now complete, and results are being published in peer-reviewed literature. Advances in personal monitoring made data collection feasible not only for healthy adults but also for children and persons with chronic heart and lung diseases. Monitoring studies of groups of individuals measured at successive points in time supported the conclusion that ambient (outdoor) particle concentrations are a key determinant of variation in personal exposure to particles. Such an association of ambient concentrations with personal PM exposures supports the use of ambient concentrations in time-series analyses and as a relevant metric for public health.

Although substantial monitoring data have been collected and analyzed, understanding remains incomplete on the quantitative relationships between outdoor measures of airborne PM and actual personal exposures to PM. Monitoring data should also be used to evaluate existing exposure models and develop new models when necessary. In addition, there is still only sparse information about the exposures of susceptible individuals for example, those with chronic heart and lung diseases to particles and other air pollutants. However, studies on such individuals might best be deferred

BOX S-1 Research Priorities and Questions Recommended by this NRC Committee

Research Topic 1. Outdoor Measures Versus Actual Human Exposures

What are the quantitative relationships between concentrations of particulate matter and gaseous copollutants measured at stationary outdoor air monitoring sites and the contributions of these concentrations to actual personal exposures, especially for subpopulations and individuals?

Research Topic 2. Exposures of Susceptible Subpopulations to Toxic Particulate Matter Components

What are the exposures to biologically important constituents and specific characteristics of particulate matter that cause responses in potentially susceptible subpopulations and the general population?

Research Topic 3. Characterization of Emission Sources

What are the size distribution, chemical composition, and mass emission rates of particulate matter emitted from the collection of primary-particle sources in the United States, and what are the emissions of reactive gases that lead to secondary formation through atmospheric chemical reactions?

Research Topic 4. Air Quality Model Development and Testing

What are the linkages between emission sources and ambient concentrations of the biologically important components of particulate matter?

Research Topic 5. Assessment of Hazardous Particulate Matter Components

What is the role of physiochemical characteristics of particulate matter in eliciting adverse health effects?

Research Topic 6. Dosimetry: Deposition and Fate of Particles in the Respiratory Tract

What are the deposition patterns and fate of particles in the respiratory tract of individuals belonging to presumed susceptible subpopulations?

Research Topic 7. Combined Effects of Particulate Matter and Gaseous Pollutants

How can the effects of particulate matter be disentangled from the effects of other pollutants? How can the effects of long-term exposure to particulate matter and other pollutants be better understood?

Research Topic 8. Susceptible Subpopulations

What subpopulations are at increased risk of adverse health outcomes from particulate matter?

Research Topic 9. Mechanisms of Injury

What are the underlying mechanisms (local pulmonary and systemic) that can explain the epidemiological findings of mortality and morbidity associated with exposure to ambient particulate matter?

Research Topic 10. Analysis and Measurement

To what extent does the choice of statistical methods in the analysis of data from epidemiological studies influence estimates of health risks from exposures to particulate matter? Can existing methods be improved? What is the effect of measurement error and misclassification on estimates of the association between air pollution and health?

Sources: NRC 1998, 1999, 2001.

TABLE S-1 EPA Funding for PM Research and Related Technical Work (in millions of dollars)

	Fiscal Year Budgets					
	1998	1999	2000	2001	2002	2003
PM research	42.0	47.3	53.7	59.0	61.1	58.1
Related technical work	8.2	8.3	8.7	6.3	6.6	8.8
TOTAL	50.2	55.6	62.4	65.3	67.7	66.9

until monitoring methods can be enhanced to characterize exposures to specific PM components.

Research Topic 2. Exposures of Susceptible Subpopulations to Toxic Particulate Matter Components

A small number of studies have included measurements of personal exposures to various particulate constituents, including sulfate, nitrate, ammonium, elemental and organic carbon, and other substances. However, research conducted to date on such exposures has focused on methods development. These efforts will be useful in initial chemical characterizations of exposure of potentially susceptible subpopulations and in directing the design of future exposure studies. However, before implementing research on this topic, the committee's sequence of research calls for substantial advances in identifying biologically relevant PM characteristics.

Research Topic 3. Characterization of Emission Sources

Although critically important for implementation of new PM NAAQS, a comprehensive and cohesive emissions characterization program (previously recommended by the committee) has not yet been implemented by EPA or other responsible sponsors, including state agencies. Characterizing PM emission sources requires accurate measurements of mass emission rates, composition, and size distributions from a representative sample of an individual source type. In addition, accurate emission rates of reactive precursor gases, such as sulfur dioxide, are needed. Since 1997, the committee has identified several advances, the greatest of which has been improvement in estimating on-road mobile-source emissions (particularly

from heavy-duty diesel trucks) of PM mass, ultrafine particles with diameters less than 0.1 μm, ammonia, and semivolatile organic vapors. Additional test methods and testing are needed for the many other sources that contribute major fractions of ambient PM (such as residential wood combustion, wildfires, cooking, and nonroad engines). Both direct and precusor sources of carbon emissions are the most poorly characterized of the emissions contributing to PM. Also, more efforts are needed to understand the uncertainties in emissions inventory estimates. As the committee emphasized in its third report, EPA should develop a comprehensive plan for systematically translating new source-test methods into a completed, comprehensive national emissions inventory based on contemporary source tests of comparable quality. The first step in planning the source-test program would involve the systematic creation of a master list of the representative sources that should be given highest priority. The timeline for this testing must allow for incorporation of revised and updated data into an overall emissions inventory of predetermined quality and completeness before the next round of PM implementation plans are drafted.

Research Topic 4. Air Quality Model Development and Testing

EPA's ultimate goal should be to have integrated, flexible, and well-tested aerosol models available for development of emission-control strategies for ambient PM management. It is still not clear that EPA is making appropriate commitments to develop models for local air quality management. Taking into consideration limited progress on emissions characterization and on source- and receptor-oriented models, the committee remains concerned about the air quality management community's access to fully operational tools for the NAAQS implementation tasks to be undertaken in the coming years.

Although instruments needed to monitor air quality are largely in place, much remains to be done if the resulting data are to be used effectively. Access to these data by researchers and other potential users outside of EPA should be made easier.[1] Users of the data also face the difficulty of accounting for substantial sampling and analytical uncertainties in the measurement of major particle components—most critically, organic material.

[1]The internet portal that once served this function has been replaced since 2001 by a notice to submit a Freedom of Information Act request to EPA to obtain hourly or daily monitoring values.

Various models earmarked for regulatory application will be operationally useful only to the extent that data needed to support them are routinely available. Characterizing emissions is a major need for both source- and receptor-oriented modeling. The rigorous evaluation of source-oriented models will also require large-scale, three-dimensional field studies, because spatially limited measurements are insufficient to challenge a model's mass accounting. Although data sets from already-completed efforts may be adequate in some locations, additional studies are needed in regions of differing climate and emissions. The committee also recognizes the need to improve bridging between geographic scales typically used for PM source-oriented modeling and those needed to conduct exposure assessment.

Although EPA alone might not have adequate resources for model evaluation, it can participate in, and coordinate, efforts involving other government agencies and private institutions with substantial field monitoring programs, enhancing such efforts in ways that synergistically increase the value of the resulting data for its own applications. EPA leadership is needed for a coordinated effort to document and compare models and to identify capabilities and limitations of models for decisionmaking purposes.

Research Topic 5. Assessment of Hazardous Particulate Matter Components

The current NAAQS for PM is both size and mass-based and implicitly assumes that all particles of a given size have the same toxicity per unit mass, irrespective of chemical composition. In the committee's judgment, this mass-based NAAQS greatly oversimplifies complex biological phenomena. Progress on assessment of hazardous PM components is central to the national research portfolio and to any refinement of the current mass-based NAAQS for PM. Without progress on topic 5, targeted exposure studies cannot be developed under topic 2, nor can emission inventories and models be refined under topics 3 and 4. Also, new information on hazardous PM components would help to guide efforts to better understand the deposition and fate of relevant particles (topic 6). Research on biological mechanisms (topic 9) and identification of susceptible populations (topic 8) could be enhanced by research accomplishments in topic 5. A better understanding of characteristics that modulate toxicity could lead to targeted control strategies specifically addressing those sources having the most significant adverse effects on public health.

The diversity of PM characteristics and the array of possible health

effects define a potentially large and complex matrix for investigation; in fact, different features of particles might be relevant to different health outcomes. Since the committee's first report in 1998, even though progress in assessing specific hazardous characteristics of PM has been fragmented, an increasing number of studies have been published that address specific characteristics of particles, including size and chemistry. The resulting evidence provides some new insights concerning toxicity for many of the specific particle characteristics related to size and chemical composition, as discussed in this report. However, there is a large variety of possible relationships between PM characteristics and health outcomes and, to date, those relationships have not been approached systematically.

Epidemiological research has been limited by the lack of detailed ambient monitoring data on particle characteristics collected over periods of time and thought to be relevant to exposure and health effects. The research has also been limited by the high correlations among some particle components. Given the complexity of the hypotheses to be tested, large data sets with rich detail on particle characteristics are needed to reduce uncertainties related to topic 5. Also, the sustained research efforts to obtain air quality monitoring data to estimate exposures for study participants and communities for epidemiological studies are only now coming into place. The initial toxicological studies are providing promising findings, pointing to possible roles for the ultrafine fraction of PM, metals, and other components of the PM mixture in air.

Despite the large number of research projects directed at this issue, progress since 1998 has been modest, reflecting the challenging set of scientific questions to be addressed. The matrix of relationships between particle composition and possible health responses has been only partially explored. Researchers have focused on PM collected from specific emission sources or on PM components of their particular interest, or they have focused on popular hypotheses or suggestive experimental evidence. A more systematic approach will be required to ensure that research encompasses a broader range of potentially important PM characteristics and yields data that can be used to establish the relative toxicity of different components.

Research Topic 6. Dosimetry: Deposition and Fate of Particles in the Respiratory Tract

Dosimetry provides a critical link between exposure to atmospheric concentrations of particles and the doses of particles reaching critical sites

in the respiratory tract, the clearance of particles from those sites, and the movement of particles from the respiratory tract to other organs. The greatest policy-relevant advance in the understanding of PM dosimetry since the committee's first report is the convergence of evidence from studies in multiple laboratories that demonstrate an increase in the portion of inhaled $PM_{2.5}$ depositing in the respiratory tracts of people having obstructive lung disease (a highly prevalent condition). The available evidence on dosimetry confirms earlier work suggesting that abnormalities of airway structure or intrapulmonary gas distribution are likely to increase the total deposited dose for a given exposure concentration.

The greater deposition fraction and the heterogeneity of deposition in abnormal lungs offer one possible mechanism for increased susceptibility of persons with underlying lung disease to inhaled particles—increased lung dose to localized lung regions—in comparison with persons having normal lungs. Differences in fractional and regional deposition associated with aging have not yet been adequately characterized. Clearance has been less well studied than deposition, and the effects of gender, age, and respiratory abnormalities on clearance remain largely uncertain. Translocation of PM or PM constituents from the lung to other organs has been demonstrated, but this phenomenon has not yet been well characterized. Evidence is more limited for specific size fractions of particles, such as ultrafine particles and particular chemical components of particles. Additionally, more information on dosimetry in animal models of human disease is needed to facilitate extrapolation of findings from these models to humans.

Research Topic 7. Combined Effects of Particulate Matter and Gaseous Pollutants

This research topic addresses the extent to which the effects of PM on health are independent of coinciding effects of other pollutants and the possibility that PM effects vary with concentrations of other pollutants. Research is complicated by the possibility that modification of the effects of PM by other pollutants could vary among health outcomes.

The committee's review found little new direct evidence related to topic 7, other than newer observational studies that have continued to demonstrate an independent effect of particles that is robust to statistical adjustment for other pollutants. Assessments of effect modification in epidemiological and toxicological studies have provided little evidence to indicate whether PM effects vary with concentrations of other major pollutants in ambient air. The committee concludes that further research is

needed to address topic 7, while acknowledging the challenges in carrying out such studies whether based on epidemiological observations or toxicological experiments.

Modification of PM effects by other pollutants, particularly ozone, can be more powerfully explored in planned larger studies, such as extensions of the approach used in the National Morbidity, Mortality, and Air Pollution Study (NMMAPS). More comprehensive characterization of mixtures considered in source-oriented exposure studies would make such studies more informative. A better understanding is needed of why some mixtures and potentially those from different sources have different effects in different diseases.

Research Topic 8. Susceptible Subpopulations

Research on susceptible populations is needed to ensure that all populations are protected against risks from PM, including those groups who might be most susceptible. There have been several new findings relevant to susceptible subpopulations. Research results show that following PM exposures,

- Persons with diabetes might be at increased risk for adverse health effects, including increased mortality.
- Persons with asthma or chronic obstructive pulmonary disease (COPD) exhibit greater deposition of inhaled fine and ultrafine PM, resulting in higher doses and associated risks.
- Older adults experience adverse changes in cardiac physiology.
- Older adults show hematological changes that are relevant to risk for cardiovascular disease (for example, changes in blood coagulation factors).

Animal models are yielding consistent findings. Dogs with coronary occlusion and hypertensive rats demonstrate adverse cardiac and vascular effects when exposed to PM. Studies involving rodent models of aging show enhanced susceptibility to PM and an increase in the effect of PM with infection.

To obtain evidence needed to understand the impacts of PM on susceptible subpopulations, research should more effectively address different time scales of exposure (from short-term peaks [acute] to long durations [chronic]), characteristics of exposure, cellular and molecular mechanisms, the range of potential adverse health effects, and potential effect modifiers.

Some current concerns focus on whether chronic PM exposures relate to the development of disease and of organ dysfunction, the extent to which ultrafine particles induce adverse effects in asthma and COPD patients, and the magnitude of life-shortening from PM exposures.

Research Topic 9. Mechanisms of Injury

The major potential biological processes suggested to underlie the reported human health effects from ambient PM exposures include oxidative stress and pulmonary or systemic inflammation. Among the postulated physiological consequences of injury by PM are increased airway hyperreactivity; alterations in the cardiovascular system, such as changes in blood viscosity, heart rate, and rhythm; and heart rate variability. Since 1997, research has broadened to address more subtle pulmonary responses relevant to current exposures and also cardiovascular responses to inhalation of PM. Investigators have begun to consider the respiratory tract as a portal of entry for particles producing systemic effects rather than simply as a target organ for PM.

Results from epidemiological, clinical and animal studies are converging to indicate that PM exposures, both to $PM_{2.5}$ and ultrafine particles, have adverse cardiovascular effects. Although research has provided some leads on potential mechanisms underlying these effects, uncertainty remains regarding the role of copollutants. It is becoming more evident from clinical and toxicological studies that ambient fine PM induces respiratory and cardiovascular events that in susceptible, compromised people can explain the morbidity and mortality observed in epidemiological studies. Research has documented that components of hypothesized mechanistic sequences do actually take place, supplying a biological basis for explaining some effects of PM observed in susceptible subpopulations.

Despite substantial research since 1997, uncertainties remain concerning potential mechanisms underlying the various adverse effects of PM observed in epidemiological studies. In part, these uncertainties reflect the limitations of extending findings from toxicological studies that by necessity use small sample sizes to human studies in which large populations are studied to detect effects. Efforts to apply toxicological findings include the challenges of extrapolating from in vitro systems and high-dose animal experiments at concentrations sometimes orders of magnitude greater than those received by people from ambient exposures. There is also uncertainty about mechanistic observations based on nonphysiological exposure routes,

such as intratracheal instillation. The next step is to more clearly understand mechanisms underlying exposure-dose-response relationships, recognizing that it is likely that most mechanisms will have some element of exposure (dose) dependence. The findings from the clinical, animal, and in vitro experimental work have often not addressed exposure-dose-response relationships, which may provide critical insights into the relevance of the experimental findings for interpreting epidemiological research. In addition, similar physiological, cellular, and molecular responses to PM in different species help to provide a mechanistic underpinning to the epidemiological observations.

Another major uncertainty relates to the lack of understanding of the relationships between the mechanisms responsible for acute versus chronic health effects. As the focus shifts to findings from epidemiological studies on chronic health effects, a similar shift will be required of the mechanistic studies. At present, it is unclear how the mechanisms characterized in the acute health-effects studies relate to the mechanisms underlying chronic health effects.

Research Topic 10. Analysis and Measurement

In its previous reports, the committee outlined several methodological issues needing further study. The issues included the sensitivity of findings in epidemiological studies to the statistical models used, the consequences of measurement error in epidemiological studies, and the analytical approaches to addressing the degree of life shortening associated with PM exposures. Since 1997, several new statistical methods have been introduced to analyze the temporal association between air quality measures and health. These models have been used to examine large national databases and to pool evidence across multiple locations. Although the committee's previous reports had found substantial progress related to this topic, recent findings on the sensitivity of time-series results to modeling approaches are an indication that further methodological research is needed. After the committee's third report, a problem was recognized in the application of a widely used statistical package in time-series analyses, resulting in extensive reanalyses of several studies that were central to characterizing the short-term risks of air pollution. These reanalyses yielded somewhat lower estimates of the effect of PM on risk for hospitalization and mortality. Nonetheless, time-series studies are likely to remain important for estimating the health effects of air pollution on populations, and a more complete

understanding of the implications of modeling approaches is needed. In adddition, the issue of "harvesting" or mortality displacement[2] needs further investigation. It would also be important to understand any relationship between the results of the times-series studies and the cohort studies.

A framework was also developed to address measurement error–the difference between the actual exposure and the measured exposures of individuals in a study. The framework implies that measurement error per se will not create the positive associations found between air pollution and health effects. More precise estimates of the magnitudes and statistical distributions of measurement error need to be incorporated into multipollutant models to provide more reliable quantitative estimates of the impact of measurement error and of the relative importance of various pollutants on health impacts. Greater consideration of this issue would give more credence to risk assessments used to support regulatory decisions.

LOOKING ACROSS THE RESEARCH TOPICS

As the context for PM research has evolved, five cross-cutting issues have emerged.

An Increasing Number of Adverse Health Outcomes Associated with PM and the Related Susceptible Subpopulations

Research results under the topics of outdoor measures versus actual human exposures, dosimetry, combined effects of PM and gaseous pollutants, susceptible subpopulations, and mechanisms of injury indicate a broadening scope of health concerns since the committee's 1998 report. At that time, emphasis was largely placed on total morbidity and mortality from respiratory causes, such as exacerbation of chronic respiratory diseases, including COPD and asthma, and the respiratory health of children. Subsequently, the list of particle-related health outcomes has broadened and now includes several adverse cardiac outcomes, such as changes in heart rate variability, cardiac arrhythmias, ischemic events, and congestive heart

[2] The terms "harvesting" or "mortality displacement" refer to questions of whether deaths from air pollution occur in people who are highly susceptible and near death (and die a few days earlier because of air pollution than they otherwise would have) or whether air pollution leads to the death of people who are not otherwise near death.

failure, as well as reproductive outcomes. Health-outcome research has also focused on many susceptible subpopulations, such as those with preexisting cardiopulmonary illnesses, children, and older adults. Although findings on several of these outcomes remain preliminary and inconsistent, interest has grown in investigating these outcomes and exploring new ones.

Particle Toxicity in Relation to Different Particle Characteristics and Emission-Source Types

Ambient particles contain a large spectrum of individual compounds. Research findings from the Supersites Program and other atmospheric characterization studies have elegantly demonstrated the complexity of ambient particle characteristics. Research to assess hazardous PM components seeks to understand the comparative toxicity of particles in relation to their specific characteristics (for example, size or composition). Information needed to relate particle characteristics to their potential health risk remains largely incomplete, and the committee views this as a critical gap. Identifying toxicity-determining components of PM is the cornerstone for moving from strategies directed at particles generally to those directed at particular sources of more toxic particles. Such information is helpful for the development of effective controls on emission sources.

Increasing Emphasis on Exposure-Dose-Response Relationships

Emphasis needs to be shifted from research directed primarily at the question of whether particles are causing particular health effects (that is, hazard identification) to characterizing exposure-dose-response relationships (that is, the form of the quantitative relationship between exposure and risk for an outcome). Knowledge of exposure-dose-response relationships is important in establishing the NAAQS for PM and implementing effective control strategies. This quantitative understanding can guide decisionmaking, offering a foundation for estimating the burden of morbidity and mortality caused by particles and comparing the benefits of alternative scenarios of air quality management. The design of research directed toward characterization of exposure-dose-response relationships may differ from that directed toward hazard identification. In particular, information on exposure-dose-response relationships is needed across a range of particle exposures relevant to those received by people at contemporary concentra-

tions. The incorporation of approaches that will allow examination of exposure-dose-response relationships for in vitro systems and laboratory animal experiments will be critical in further research evaluating the comparative toxicity (potency) of PM components.

Considering PM Health Effects within the Broader Context of Other Pollutants in the Ambient Air

For some time, investigators have recognized that surrogates for "dirty air" have been derived from assessing one pollutant at a time, and possible health effects attributed to a single pollutant have often been used in part to make regulatory decisions. However, in recent years, scientists and regulators have been concerned that, except in specific occupational settings, humans are exposed to air pollutant mixtures. In addition, the recognition of a broader range of health impacts as being putatively related to ambient pollution raises the possibility that single pollutants may be acting together to increase risk through interactive mechanisms. Research findings on the combined effects of particles and gaseous copollutants, susceptible populations, mechanisms of injury, and human exposures have implications that extend beyond PM. The finding of interactions between PM and the other five criteria pollutants listed in the Clean Air Act could provide a rationale for more integrated standards reflecting realistic atmospheric mixture exposures to populations at risk and reflecting the potential for overall mixture toxicity.

Designing PM Research Programs to Inform Most Effectively the Setting and Implementing of the PM NAAQS

Important PM research needs have implications for the setting of the PM NAAQS. Research results on exposure assessment, emissions characterization, development and testing of air quality models, assessment of hazardous PM components, assessment of the combined effects of PM and gaseous pollutants, and understanding the mechanisms of injury may have significant impacts on the four elements of the NAAQS for PM, namely, the pollutant indicator, averaging time, numerical level of the indicator, and the statistical form of the standard. Measurements of source emission rates for PM and precursor gases as well as evaluations of models are needed as states begin the process of developing NAAQS attainment plans.

CHALLLENGES FOR THE YEARS AHEAD

In 1998, the committee recognized that meeting its research agenda would require a substantial investment as well as development of new research approaches to address complex scientific questions. In reviewing work carried out since its first report, the committee has identified seven remaining scientific challenges that should be of highest priority in further work to complete the PM research agenda. These challenges are central to the PM research agenda; meeting them may require the development of new research approaches and research management strategies.

Completing PM Emissions Inventory and Air Quality Models Necessary for NAAQS Implementation

Although the committee's charge is to provide independent guidance for planning and monitoring a long-term PM research program, it recognizes that this research program will also provide the tools needed for implementation of current and possible future PM NAAQS. In particular, improved emissions characterization and air quality model testing and development are critical for state implementation plans (SIPs) that detail steps that states and local air districts will use to attain the $PM_{2.5}$ NAAQS. Although some positive steps have been taken by EPA, rapidly approaching SIP deadlines require faster progress to ensure that these plans are based on the best available information. Research to improve emission inventories and air quality models will also support more targeted emission-control strategies as progress is made in characterizing hazardous PM components.

The specificity of the PM NAAQS on the solid phase of ambient pollutants poses significant scientific challenges for source-test methods. The partitioning of many substances between gas and particle phases is sensitive to environmental parameters, such as temperature and humidity, which typically differ greatly between effluent and ambient conditions. Emission-test methods have historically paid limited attention to such distinctions, thereby yielding particulate emission rates of uncertain relevance to ambient conditions. In its second report, the committee stressed the need for developing new dilution-based source-test methods that simulate ambient conditions and for systematically applying these to a wide array of sources. Implementation of PM NAAQS will require comprehensive national and local emission inventories of PM mass emission rates, composition, and size distributions, along with emission rates of reactive

precursor gases (sulfur dioxide, oxides of nitrogen, ammonia, and volatile organic compounds). These inventories will in turn require measurements relevant to ambient conditions as a representative sample of an individual source type.

Understanding the relationships between emissions and ambient concentrations is also central to regulatory decisionmaking. The committee is concerned that implementation of emission controls to attain PM standards may rely on untested air quality models. There appears to be a tendency to view model development as a research activity that can be decoupled from the regulatory support functions of ambient monitoring and emissions tracking. However, emissions, ambient concentrations, and source-receptor relationships are closely interrelated in certain situations (as when a known source dominates ambient loadings); in such circumstances, there is an opportunity for cross-calibration and verification. The three activities of emissions tracking, air quality modeling, and ambient monitoring need to be viewed as elements of an integrated process. The committee recommends that the EPA PM program better acknowledge these interrelationships to promote iterative improvements in emission inventories, monitoring networks, and air quality models.

Developing a Systematic Program to Assess Toxicity of PM Mixture Components

This pivotal topic carries implications not only for research directions but also for PM-control strategies. Answering the key questions concerning hazardous components of PM will require a carefully coordinated, long-term multidisciplinary research effort that goes well beyond the work now under way. Although substantial relevant research has already been carried out, the committee's review showed a diffuse assemblage of evidence with little convergence. Also, the use of disparate approaches to assess hazardous PM components by investigators in the diverse research communities has been a barrier to interpreting the resulting evidence.

The research strategy for addressing this topic should be reconsidered, moving from solely investigator-initiated approaches toward more carefully structured ones. A more systematic evaluation of PM by characteristics, components, and health outcomes should be combined with investigator-initiated research that may follow resultant leads or focus more deeply on specific hypotheses. There is also a need for coherent and converging evidence from exposure and atmospheric characterization and from toxicological and epidemiological research that addresses specific components

and health outcomes in parallel. Such integrative research would facilitate judging the extent to which toxicological observations, particularly those made at higher doses, can be generalized. This type of orchestrated programmatic research might be conducted by EPA, through the resources of the EPA PM research centers, or through other research mechanisms.

Barriers to implementing integrated research include scientific and administrative challenges. There is also a need to foster cross-disciplinary communication and collaboration. The costs for the needed research may substantially exceed those originally estimated for this topic by the committee, but these costs should not be a basis for deferring needed research, given the importance of the air pollution control topic.

Enhancing Air Quality Monitoring for Research

Meeting the key PM research priorities will require a shift in the current air monitoring paradigm, from primarily assessing compliance with the NAAQS toward serving multiple purposes, such as air quality forecasting, episode alerts, exposure characterization in populations at high risk, health studies, atmospheric process studies, evaluating emission-source zones of influence, and evaluating long-term effectiveness of control strategies. This shift implies less use of federal reference methods at urban locations and greater use of in situ continuous monitors and compound-specific integrated samples at locations representing background, boundary, transport corridor, regional, urban, and neighborhood spatial distributions.

Such an enhanced network should use continuous measures of appropriate indicators with real-time access, attempt to represent less-uniform micro- and middle-scale exposures, and encourage the completion of development of continuous monitors for indicators other than mass concentrations.

A carefully designed network serving multiple purposes could be accomplished using the same resources currently dedicated to compliance monitoring that would have much greater public-health and knowledge-creation benefit than the current filter-based network.

Investigating the Health Effects of Long-Term Exposure to Air Pollution

Long-term epidemiological studies are likely to remain central in assessing the public-health burden caused by air pollution. For quantitative risk assessment and cost-benefit analysis, estimates of the disease burden associated with exposure to particles are needed, and research approaches

should continue to be developed on the basis of existing and new cohorts. Mechanisms are needed for enrollment and tracking of cohorts, including their exposures and health outcomes, that would provide an ongoing characterization of any impact of long-term exposure to air pollution on health.

It is not yet clear what role chronic exposure studies (that is, encompassing most or all of the life span) of animals could play in predicting human health effects or in enhancing the understanding of the mechanisms and exposure-dose-response relationships of long-term exposure to PM. A likely application of toxicological research to understanding the consequences of long-term human exposures to PM lies in the use of studies incorporating repeated exposures ranging from several days to a few months. Intermediate-term studies could help characterize long-term study needs and designs.

Improved Toxicological Approaches

The committee has previously recognized the need for complementary epidemiological and toxicological evidence. Toxicological approaches have been limited by the difficulty of replicating real-world inhalation exposures to PM in terms of chemistry, by the relatively high doses often used in animal studies, by the common use of instillation rather than inhalation of the particles, and by the inability to readily replicate human diseases associated with increased susceptibility. Using toxicological approaches to assess hazardous PM components has also proved to be especially challenging. Separating the potential effects of particle size from those of particle chemistry is difficult, because particles of different size might have different chemical characteristics and different rates or routes of clearance, which affect responses. Studies of appropriate design are needed, as are well-characterized particle samples for experimental exposures.

From a Particulate Matter Research Program to a Multipollutant Research Program

Another challenge to completing the committee's research agenda lies in the scientifically artificial separation of research on PM from research on air pollution generally. This separation follows the regulatory approach of setting ambient standards for six individual criteria pollutants and corresponding emission standards on precursors without adequate recognition of

their interrelationships in determining their risk to health. Given the need to develop the evidence base for the NAAQS, research has too often been driven by a schedule reflecting the regulatory cycle of NAAQS review and by the scope of research being restricted to single pollutants rather than the air pollution mixture.

Although the PM research agenda has appropriately considered other pollutants, it has of necessity been directed at PM. Researchers have considered some other air contaminants, largely other criteria pollutants, as "copollutants" for their potential impact on PM effects. This research tests whether PM effects depend on the presence or concentrations of other pollutants without considering the overall toxicity of the air pollution mixture, as the characteristics of the mixture vary. For the future, there is an opportunity and a critical need to shift from the current single-pollutant focus to a multipollutant focus that begins by acknowledging that real-world exposures involve complex mixtures of hundreds of air contaminants falling into several physical-chemical classes.

A multiple air pollutant program can be carried forward in a manner that reflects the need to develop information relevant to the setting of standards and the development of air quality management strategies. It is important that research priorities be carefully established in such a research program. One potential payoff of a multipollutant science-based approach is the high likelihood that the resulting information will aid in understanding the relative importance of various pollutants (and thus sources) and their interactions in causing adverse health effects. This knowledge should have clear benefit in optimizing both the cost-effectiveness and the health benefits of future air quality management strategies.

Integrating Across Disciplines

The need for complementary evidence on PM from multiple disciplines was recognized early by the committee. It called for interdisciplinary research and proposed the PM research centers as one mechanism for fostering interdisciplinary collaboration. Although greater cross-disciplinary integration has occurred in some PM research topics, to a large extent the coordination of toxicological, epidemiological, exposure, and atmospheric research has received more discussion than actual implementation to date. Expanding multidisciplinary strategies and programs will be essential to implement a multipollutant approach.

At a minimum, such efforts should include the following:

- Active collaborative research design.
- A shift by funding agencies toward giving higher priority to research implemented by truly multidisciplinary teams.
- Adequate research funding for projects to allow the active involvement of a full team (including senior investigators from multiple disciplines, if needed).
- Fellowships or sabbaticals that will enable scientists to collaborate with groups outside their disciplines.
- Redoubled efforts of appropriate professional societies to hold joint workshops and meetings and to publish proceedings.

MANAGING SCIENCE TO ADDRESS THE KEY REMAINING QUESTIONS

Progress to date on several of the committee's priority research topics is encouraging and demonstrates that key uncertainties can be quickly addressed with targeted research initiatives, as in the example of research on outdoor measures of airborne PM versus actual human exposure (research topic 1). The committee has been impressed by EPA's quick incorporation of the PM research portfolio into its planning and its integrated approach to managing PM research within the agency. It is not surprising that much research remains to be done from the committee's original research agenda, as detailed in this report, and new research findings always invite new questions.

Beyond continuing to seek answers to those specific questions, the committee has identified some recent progress to address the seven challenges discussed above (for example, implementation of the nationwide speciation monitoring network), but those seven issues need careful attention as the PM research program continues. By addressing these challenges directly, the pace of scientific gain should be quickened and the quality of research evidence strengthened.

These challenges also pose significant challenges to the management of scientific research. To address them effectively, a series of steps should be taken to effectively manage this complex scientific enterprise:

First, an even higher level of sustained integration and interaction will be needed to successfully complete the research portfolio. This step must be taken among the scientific disciplines and among the full range of public and private research funding organizations.

Second, much stronger tools will be necessary to compile and synthesize

the large amounts of new information being developed in this research program.

Third, and perhaps most important, sustained and substantially enhanced management of this program by EPA, accompanied by a continuing mechanism for independent review and oversight of the program, will be the only way to ensure that this investment is being soundly made. EPA has taken steps toward better management, but recent frequent transitions in management personnel of that effort and a substantial need for new management systems and administrative mechanisms for supporting research—especially on the topic of assessment of hazardous PM components—suggest that EPA will need to enhance its efforts. Also, it will be important to develop some form of continuing independent oversight to provide continued monitoring and guidance for EPA's and others' efforts.

Much has been learned from the research investment since 1998, and evidence gained by the investment is already being used in decisionmaking, which will continue even in the face of uncertainty. However, much is still to be learned. A failure to invest in developing greater understanding of the effects of PM and air pollution, in general, on health would result in not taking full advantage of the substantial research investment to date and in limiting the nation's ability to make evidence-based health policy and air quality regulatory choices in the future. Alternatively, continued enhancement of the air pollution and health research effort will undoubtedly yield substantial benefits for years to come. It is clearly the latter choice that offers the most promise to the nation in its effort to improve air quality and public health.

1

Introduction

COMMITTEE'S TASK

This is the fourth and final report of the National Research Council (NRC) Committee on Research Priorities for Airborne Particulate Matter. The committee was convened in January 1998 at the request of the U.S. Environmental Protection Agency (EPA) pursuant to directions from Congress in EPA's fiscal year 1998 appropriations report. The congressional request for this independent NRC study arose from a need to address scientific uncertainties surrounding EPA's July 1997 decision to establish new National Ambient Air Quality Standards (NAAQS) for airborne particulate matter (PM) smaller than about 2.5 micrometers (μm) in aerodynamic diameter (EPA 1997).[1] Contemplating the review of the PM NAAQS in 2003 and every 5 years thereafter, as well as EPA's proposed schedule for regulatory implementation of the new standards, Congress mandated and appropriated substantial funds for EPA to conduct a major research program to reduce scientific uncertainties. It also directed the EPA Administrator to arrange for the NRC to provide independent guidance for planning the research program and monitoring its implementation. Specifically, the committee was charged with assessing research priorities, developing a conceptual research plan, and monitoring research progress made over 5

[1] PM_{10} refers to particulate matter collected by a sampling device with a size-selective inlet that has a 50% collection efficiency for particles with an aerodynamic diameter of 10 μm. $PM_{2.5}$ is similarly defined except with reference to a 2.5-μm size cut. Total suspended particles (TSP) refers to the particle mass collected up to a range of 25-50 μm aerodynamic diameter.

years (1998-2002) in understanding the relationships among airborne PM, its various sources, and its effects on public health.[2] The committee's formal statement of task is presented in Appendix B.

This final report of the committee addresses progress since its first report, published in 1998 (NRC 1998). That report, *Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio*, proposed a conceptual framework for a national program of PM research (Figure 1-1); identified 10 high-priority research topics linked to key policy-related scientific uncertainties (Box 1-1); and presented a 13-year integrated "research investment portfolio" containing recommended short- and long-term phasing of research and estimated costs of such research. This fourth report assesses progress on the research agenda set out in the portfolio and offers an enhancement of the portfolio and recommendations for follow-up monitoring, oversight, and evaluation as research on PM extends beyond the time-frame of this committee.

This report also draws on the committee's second and third reports, published in 1999 and 2001, respectively. In its second report, *Research Priorities for Airborne Particulate Matter: II. Evaluating Research Progress and Updating the Portfolio*, the committee described its initial plans for monitoring the progress of research (NRC 1999). In addition, it reviewed and updated the research recommendations from the committee's first report and substantially revised two of the recommended research topics related to emissions characterization and air pollution modeling.

The third report, *Research Priorities for Airborne Particulate Matter. III. Early Research Progress*, provided an overview of progress through approximately mid-2000 on the research agenda (NRC 2001). In preparing that report, the committee attempted to catalog the major studies that had been initiated subsequent to its first report, as well as ongoing but relevant studies that were started before the first report. Its review covered research funded by EPA, the Health Effects Institute, and several other agencies that were supporting research on PM. The committee found substantial progress on several research topics, particularly studies directed at assessment of exposure to $PM_{2.5}$ (research topic 1) and methodological issues (research topic 10). Progress and planning were particularly lacking for research

[2]In addition to effects on human health, airborne particles have other important effects, such as reduction of atmospheric visibility, and interference with particle borne nutrients that can affect ecosystem and agricultural productivity. However, the work of the committee has been directed solely on research that elucidates the human health effects of PM.

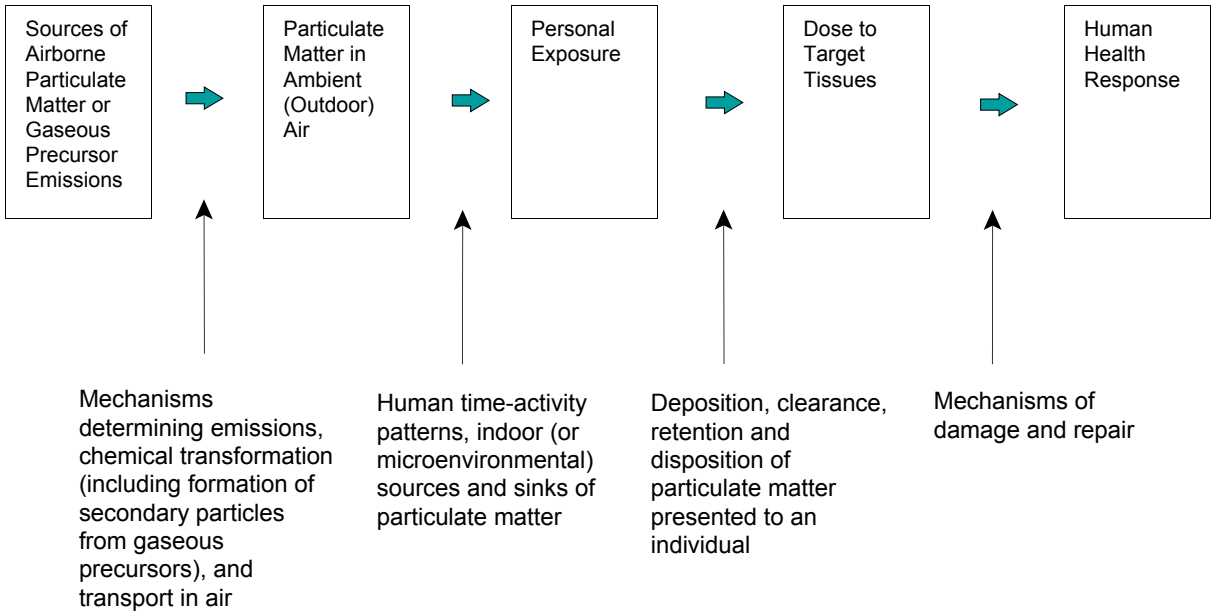

FIGURE 1-1 A general framework for integrating particulate matter research. This figure is not intended to represent a framework for research management. Such a framework would include pathways for the flow of information. Sources: Modified from NRC 1983, 1994; Lioy 1990; and Sexton et al. 1992.

BOX 1-1 Research Priorities and Questions Recommended by This NRC Committee

Research Topic 1. Outdoor Measures Versus Actual Human Exposures
What are the quantitative relationships between concentrations of particulate matter and gaseous copollutants measured at stationary outdoor air monitoring sites and the contributions of these concentrations to actual personal exposures, especially for subpopulations and individuals?

Research Topic 2. Exposures of Susceptible Subpopulations to Toxic Particulate Matter Components
What are the exposures to biologically important constituents and specific characteristics of particulate matter that cause responses in potentially susceptible subpopulations and the general population?

Research Topic 3. Characterization of Emission Sources
What are the size distribution, chemical composition, and mass emission rates of particulate matter emitted from the collection of primary-particle sources in the United States, and what are the emissions of reactive gases that lead to secondary formation through atmospheric chemical reactions?

Research Topic 4. Air Quality Model Development and Testing
What are the linkages between emission sources and ambient concentrations of the biologically important components of particulate matter?

Research Topic 5. Assessment of Hazardous Particulate Matter Components
What is the role of physiochemical characteristics of particulate matter in eliciting adverse health effects?

Research Topic 6. Dosimetry: Deposition and Fate of Particles in the Respiratory Tract
What are the deposition patterns and fate of particles in the respiratory tract of individuals belonging to presumed susceptible subpopulations?

Research Topic 7. Combined Effects of Particulate Matter and Gaseous Pollutants
How can the effects of particulate matter be disentangled from the effects of other pollutants? How can the effects of long-term exposure to particulate matter and other pollutants be better understood?

Research Topic 8. Susceptible Subpopulations
What subpopulations are at increased risk of adverse health outcomes from particulate matter?

Research Topic 9. Mechanisms of Injury
What are the underlying mechanisms (local pulmonary and systemic) that can explain the epidemiological findings of mortality and morbidity associated with exposure to ambient particulate matter?

Research Topic 10. Analysis and Measurement
To what extent does the choice of statistical methods in the analysis of data from epidemiological studies influence estimates of health risks from exposures to particulate matter? Can existing methods be improved? What is the effect of measurement error and misclassification on estimates of the association between air pollution and health?

Sources: NRC 1998, 1999, 2001.

topics 3 and 4 characterization of emission sources and air quality model development and testing, respectively.

Evidence was still insufficient for the committee to predict the program's likely effectiveness in reducing uncertainty. Overall, the committee found that the pace of implementing new research projects was slower than the original timelines envisioned in its first report, likely reflecting the practical constraints on planning, funding, and implementing major scientific research projects. Nonetheless, the committee concluded that much research was in progress in accordance with its portfolio and that EPA was responsive in following the committee's research agenda. Because research results were coming more slowly than originally expected, the committee observed that managers of the research program would probably need to adjust the timing of future research activities as they followed the sequence of the portfolio.

For this fourth report, the committee builds on the framework developed in the prior three reports. Its approach to identifying completed, initiated, or planned research and to evaluating progress is described in the second chapter. This approach incorporates the three criteria used for developing the original research agenda (scientific value, decisionmaking value, and feasibility and timing) and the three set forth in the second report for tracking implementation and progress (multidisciplinary interaction, integration and planning, and accessibility of information). The committee searched widely and comprehensively, but not exhaustively, to identify research in progress and research findings for this report, using various methods, such as workshops, literature reviews, research publications considered for EPA's PM "criteria document" (EPA 2002, 2003a), and the PM research inventory database, which was developed by the Health Effects Institute in collaboration with EPA.

STATUS OF THE EPA REVIEW OF THE NAAQS FOR PARTICULATE MATTER

As this report was being prepared and reviewed, EPA was continuing its process of reviewing the scientific evidence on PM. This lengthy process is based on detailed consideration of the scientific evidence, which is compiled in a criteria document, an encyclopedic document prepared by EPA with assistance from the larger scientific community. EPA reviews the peer-reviewed publications that are relevant to the NAAQS, focusing on those published since the last review. The "staff paper," prepared by EPA's Office of Air Quality Planning and Standards, translates the scientific advances into potential policy options, including possible revisions to the

four elements of the NAAQS: (1) the pollutant indicator (such as $PM_{2.5}$), (2) the concentration of the indicator in the air, (3) the time over which measurements are made or averaged, and (4) the statistical form of the standard used to determine the allowable number of exceedances. The staff paper references only those papers cited in the criteria document that specifically affect the setting of the four elements of the NAAQS. The criteria document and the staff paper are reviewed by EPA's Clean Air Scientific Advisory Committee.

The proposed schedule has been slowed by the magnitude of the task of preparing and reviewing the criteria document and by the identification of a substantive statistical issue affecting the results of the time-series epidemiological studies,[3] necessitating reanalysis of major studies considered by EPA (HEI 2003). The current schedule is to finalize the criteria document in 2004, release a first-draft staff paper for review in 2004, and decide whether to revise the PM NAAQS within a year of the release of the final version of the staff paper. The next complete review would follow in 5 years. Given the pace of the NAAQS review, the committee was unable to track the influence of new research on the recommendations of the staff paper.

THE NEED FOR RESEARCH ON PARTICULATE MATTER

When Congress asked the NRC to establish this committee, it recognized the continuing scientific uncertainties in the evidence that led to the 1997 revision of the NAAQS for PM and the need for gains in scientific understanding necessary for implementing the NAAQS. It anticipated the reduction of uncertainty by additional research and saw a clear need for greater certainty, given the effort and cost of implementing the NAAQS revisions. This committee's research framework was intended to be responsive to the call from Congress, and its research portfolio was structured around key sources of uncertainty. Moreover, the research findings were expected to facilitate the development of the implementation program and enhance its effectiveness in reducing PM emissions.

To reduce the uncertainties about airborne PM, research evidence is needed that fills in data gaps related to the scope of PM health effects and to the underlying processes by which PM exposure causes health effects.

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[3]Time-series epidemiological studies evaluate associations between changes in health effects and changes in exposure indicators (for example, ambient PM concentrations) preceding or simultaneous with the observed outcome.

Research evidence is also needed that addresses the links from emission sources to human exposures, particularly for those particles found to be injurious to health. The needed research is inherently multidisciplinary, involving engineers, atmospheric scientists, exposure assessors, toxicologists and other basic scientists, epidemiologists, and clinicians. Research topics 1 and 2 are largely the domain of exposure assessors but often with input from atmospheric scientists and epidemiologists. Topics 3 and 4 are of concern to atmospheric scientists and engineers. Topics 5, 7, and 8 need parallel investigation by epidemiologists and toxicologists, and topic 9 involves laboratory-based and clinical toxicological approaches, along with parallel population approaches by epidemiologists. Topics 6 and 10 call for specific disciplinary expertise. Dialogue is needed among these investigative communities, if the overall goal of reducing uncertainty within an integrated paradigm, like that proposed by the committee, is to be achieved.

Challenges in carrying out this research agenda are evident. Research evidence on PM in support of setting the NAAQS is almost inevitably subject to uncertainties, reflecting the dissonance between the complex nature of exposures of the population to multiple air pollutants and the setting of a pollutant-specific NAAQS. Air pollution in both urban and nonurban settings is a complex mixture of gaseous and solid pollutants, having both natural and anthropogenic sources. Many sources of PM also emit gases so that concentrations of PM and other criteria pollutants[4] are often correlated to a substantial degree. Motor vehicles, for example, emit oxides of nitrogen and volatile organic compounds, which contribute to secondary particle formation and which also have adverse health effects. Particles are diverse in physical and chemical characteristics, depending on their sources and atmospheric conditions.

Beyond the science needed to better inform the decisions on the PM NAAQS, the committee's research portfolio was also designed to improve the scientific basis for the large number of decisions that will be needed to implement the PM NAAQS. Improvements that need to be achieved include better measurement and characterization of both ambient PM and PM

[4]The Clean Air Act requires EPA to set NAAQS for certain pollutants known to be hazardous to human health and the public welfare (for example, damage to forests and degradation of atmospheric visibility). EPA has identified and set standards to protect human health and public welfare for six pollutants: ozone, carbon monoxide, particulate matter (PM_{10} and $PM_{2.5}$), sulfur dioxide, lead, and nitrogen dioxide. The term criteria pollutants derives from the requirement that EPA must describe the characteristics and potential health and welfare effects of these pollutants. It is on the basis of such criteria that NAAQS are set or revised.

from specific sources; models that can accurately identify the sources of particles to inform the development of national, state, and local plans for reductions; and enhanced toxicological and epidemiological study on the effects of the different sources and components of the PM mixture to assist in setting future reduction priorities. These gains in knowledge are needed for the implementation of any NAAQS; in the case of PM, they are critical because of PM's unique nature among criteria pollutants as a complex mixture of particle sizes, characteristics, and constituents. Although some work is under way in these areas, much remains to be done as the nation moves toward implementation of the PM NAAQS.

Characterizing Particulate Matter

In attempting to link sources to effects to support the development of NAAQS (Figure 1-1), PM is generally considered within a variety of particle-size categories. These size categories have been considered to have biological significance, although characteristics of particles other than size are likely to be relevant to determining their toxicity. Particle composition and the potential for particles to impact onto surfaces can vary within and across particle-size categories. The types of particles within specific size categories may also be affected by the concentrations of various gaseous pollutants in the air. Further, the size and shape of inhaled particles influence where and how much mass will be deposited in various regions of the respiratory system. The size categories most commonly distinguished in health-related research are

- PM: mixtures of any or all sizes.
- $PM_{0.1}$: particles less than about 0.1 μm in aerodynamic diameter, called ultrafines.
- $PM_{2.5}$: particles less than about 2.5 μm in aerodynamic diameter, called fine particles.
- PM_{10}: particles less than about 10 μm in aerodynamic diameter.
- $PM_{10\text{-}2.5}$: particles between 2.5 and 10 μm in aerodynamic diameter, called coarse particles.
- PM_{10+}: particles greater than 10 μm in aerodynamic diameter.

Assessing the health effects of PM is complicated by the diversity and richness of particles typically present in ambient air. Compared with a gaseous pollutant, whose effects at a given time and place are uniquely determined by its concentration, PM is only loosely defined. In concept, PM is whatever material is carried by suspended liquid and solid particles

of diverse size, shape, and composition. Some of the PM is in dynamic chemical equilibrium with the surrounding mixture of gases. As illustrated in Figures 1-2 and 1-3, characterizations of individual particles cover a heterogeneous collection of material.

In setting NAAQS in recent decades, EPA has attempted to distinguish more-hazardous from less-hazardous PM by reference to aerodynamic behavior as an indicator of particle size. Thus, PM_{10} and $PM_{2.5}$ are defined in terms of filter samples collected with the use of size-selective inlets passing 50% of particles (approximated by spheres of 1 g/cm^3 density) of 10 μm or 2.5 μm diameters. As Figure 1-4 indicates, observed particle diameters range over several orders of magnitude, with those below about 0.05 μm typically dominating particle number in urban air, those below about 0.5 μm dominating particle surface area, and those at about 10 μm dominating particle volume (or mass). The existing distinctions at 10 μm and 2.5 μm have dosimetric significance and hint at generic categories of origin, because combustion-generated particles tend to be smaller than 2.5 μm and mechanically generated dust grains tend to be larger. Figure 1-2 shows clearly, however, that particles of similar sizes can have widely differing origins and composition.

More refined categorizations can be based on chemical analyses of PM sampled by various methods, with or without aerodynamic sorting by size. Analytical strategies range from a focus on major mass fractions, often broadly defined, to targeted studies of biologically relevant species or properties or to comprehensive efforts to resolve trace elements and compounds indicative of specific emissions. Trade-offs are of course inevitable among the many possible dimensions of resolution—in time, space, particle size, and physical state and in elemental and molecular composition (McMurry 2000).

The descriptive frameworks that emerge directly from aerodynamic classification and chemical analysis are not necessarily the ones best suited to assessments of health effects or emissions management strategies. Generic types of emissions, such as diesel exhaust particles (DEP) or residual oil fly ash (ROFA), may consist of chemically complex particles over a broad range of sizes whose statistical distributions in the aggregate are, nonetheless, reasonably uniform and unvarying. Therefore, the degrees of freedom actually exhibited by ambient PM for testing hypotheses might be significantly fewer than the number of chemical components and size classes required for its detailed description. A given sample of PM can be described by a variety of different schemes of characterization, some better suited to different purposes—for example, source characterization or assessment of risks to health.

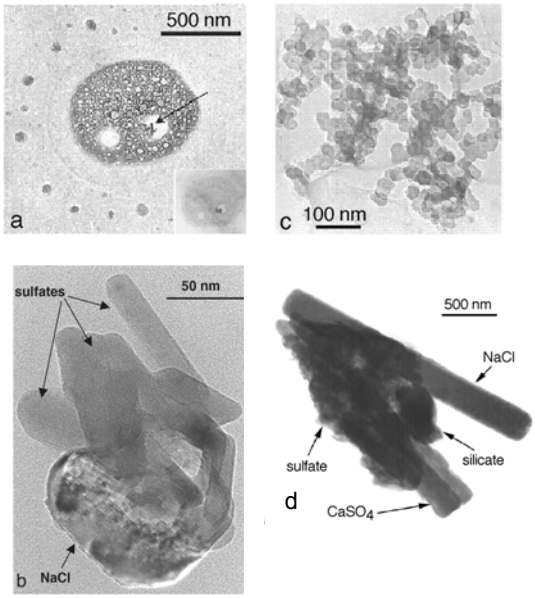

FIGURE 1-2 Electron micrographs of atmospheric particles. (a) Internal mixture of sulfate and soot; arrow points to a soot aggregate. The surrounding halo is ammonium sulfate crystals formed as the sulfate dehydrated in the microscope's vacuum. (b) Sea salt. (c) Branching soot aggregate typical of some combustion processes. (d) Internal mixture of terrestrial silicate with sea salt and anhydrite (calcium sulfate [$CaSO_4$]) likely formed by reaction of sulfur dioxide with carbonate particles. Source: Buseck and Posfai 1999.

The multiplicity of legitimate descriptive frameworks for PM is easily overlooked in interdisciplinary conversations, particularly once specific indices, such as $PM_{2.5}$, have been singled out in NAAQS and other regulatory settings. The complexity of the particle mixture nevertheless requires explicit acknowledgment if the needed integration of research is to be achieved.

Research Approaches

Many exposure assessment studies have now been carried out to measure personal exposures of people to particles and to understand the relationship between personal exposures and concentrations of particles recorded at centrally sited monitors. These studies have proved feasible,

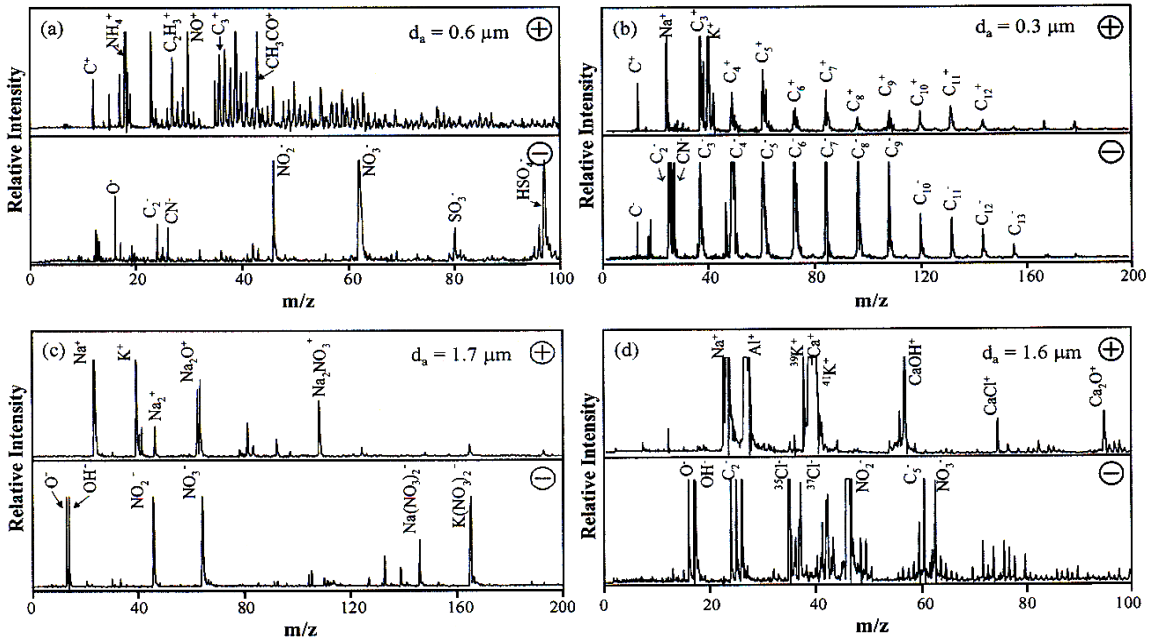

FIGURE 1-3 Positive and negative ion mass spectra obtained by aerosol time-of-flight mass spectrometry (ATOFMS) for typical individual particles in the San Joaquin Valley of California. (a) Carbonaceous particle containing sulfates and nitrates of presumably secondary origin. (b) Elemental carbon particle. (c) Sodium-containing particle likely formed by reaction of sea salt with gas-phase nitrogen oxides and sulfuric acid. (d) Calcium-rich dust particle. (See also Figure 6 in Whiteaker et al. [2002].) Source: Whiteaker et al. 2002. Reprinted with permission; copyright 2002, American Chemical Society.

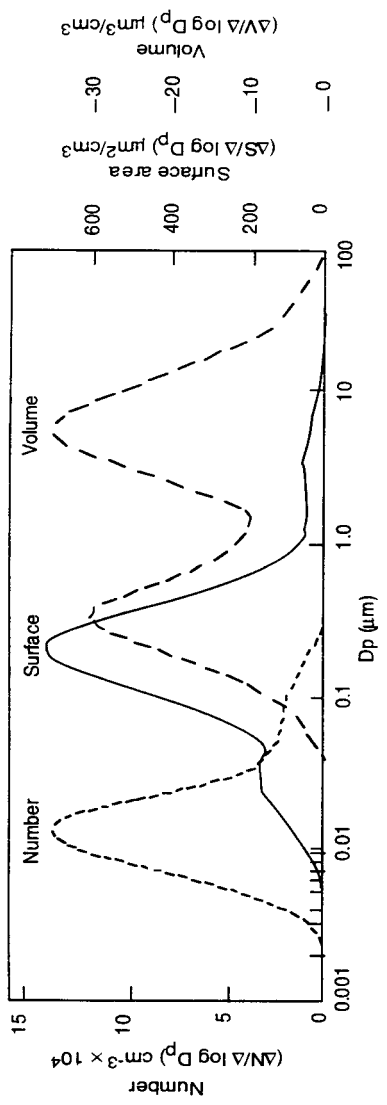

FIGURE 1-4 Average particle size distribution representative of Los Angeles smog during August-September 1969. The distribution is plotted as a fraction of total particle number, total particle surface, and total particle volume. Dp refers to the diameter of a particle. Source: Adapted from Whitby et al. 1972.

but some of the groups considered most susceptible—persons with advanced chronic heart and lung diseases—are not yet well studied. Additionally, the extent to which findings from any particular location can be generalized is uncertain, and many studies to date have focused primarily on total particle mass, rather than more detailed particle characteristics, such as their chemical composition.

Epidemiological studies take advantage of naturally occurring variation in exposure, across groups or over time, to estimate the effect of PM on one or more health outcome indicators. In an effort to provide evidence relevant to the NAAQS for PM, epidemiologists design studies that have the potential to estimate the effect of PM without contamination (confounding) by the effects of other pollutants. This approach implicitly assumes that inhaled particles have effects on health that are independent of other pollutants, an underlying assumption in having a NAAQS for PM. Alternatively, the effect assigned to PM may reflect the total effect of the air pollution mixture or some other factor that varies with PM, and PM is serving as a surrogate index. Even with careful design and analysis, there is the possibility of some residual confounding of the effect of PM by other pollutants or other factors. Some epidemiological studies take advantage of historical data on air quality and community health. Other studies use air quality and health data collected prospectively to address specific hypotheses.

Controlled human exposure studies offer the opportunity to study small numbers of human subjects under carefully controlled exposure conditions and gain valuable insights into both the relative deposition of inhaled particles and the resulting health effects. Individuals studied can range from healthy people to individuals with cardiac or respiratory diseases of varying degrees of severity. In all cases, the specific protocols defining the subjects, the exposure conditions, and the evaluation procedures must be reviewed and approved by institutional review boards providing oversight for human experimentation. The exposure atmospheres studied vary, ranging from well-defined, single-component aerosols (such as black carbon[5] or sulfuric acid) to atmospheres produced by recently developed particle concentrators, which concentrate the particles present in ambient air. The concentrations of particles studied are limited by ethical considerations and by concern for the range of concentrations, from the experimental setting to typical ambient concentration, over which findings need to be extrapolated.

Toxicological studies with laboratory animals provide the opportunity

[5]"Black carbon" is a general term that is often used interchangeably with "elemental carbon" or "soot."

to develop information under defined experimental conditions that will complement the data from epidemiological studies or controlled exposures of human subjects. The results of such studies introduce the issue of the validity of extrapolations from laboratory species to people. Nonetheless, by careful selection of the animal species and strain, including genetically modified animals, and appropriate experimental manipulation, certain aspects of both normal and diseased states in people can be reproduced in the laboratory animals. As a corollary to animal studies, in vitro exposure studies can be performed.

As in the controlled human exposure studies, a range of exposure atmospheres can be studied. The goal of the studies is not necessarily to recreate the complex mixtures of pollutants to which people are exposed in their daily lives. Rather, as in studies of diluted emissions from a specific source, such as a diesel engine, the intent is to attempt to derive some understanding about the influence of emissions from that source on health outcomes. In other cases, one or a few types of atmospheres, including specific forms of PM, such as black carbon or residual oil fly ash, have been studied. Ultimately, through the study of particles with varied characteristics, including particle size and chemical composition, insight can be gained into the extent that responses are generic or specific to particle size and composition. To enhance the potential for observing effects and thereby increase the efficiency of the research, the exposure concentrations used in toxicological studies are typically greater than those to which people are usually exposed. Particle concentrations have been used that allow the study of increased concentrations of ambient PM. Some toxicological studies have been conducted in the field at sites near particular sources, such as freeways. Such field studies come with the challenge of ensuring that the experiments are not complicated by confounding factors, such as the occurrence of infectious diseases or not readily controlled factors not usually encountered in the laboratory.

RESEARCH ON PARTICULATE MATTER

In response to the need for further research on PM, a substantial national program was initiated, largely following the 13-year research portfolio set out over 5 years ago by this committee. The committee's research investment portfolio for fiscal years 2000-2010 is shown in Table 1-1, and its estimates for technical support are presented in Table 1-2. This is the same portfolio shown in the committee's second report (NRC 1999). Available time and resources did not allow the committee to provide a detailed review and update of the research portfolio. Much of the research

has been carried out by EPA investigators, but many scientists from academia and research institutes have also been involved. In addition, a number of federal agencies formed the PM Research Coordination Working Group under the auspices of the Air Quality Research Subcommittee of the Committee on Environment and Natural Resources (CENR 2002). The working group formed an overall federal PM research strategy, and several agencies developed agency-specific strategies to guide their internal and external programs. Responding to the same need for additional evidence, other organizations in the United States have developed research programs, and the European Union and other countries have also supported research on PM. Although not readily estimated, the total funding is substantial. EPA, for example, has funded a total of $368 million on PM research and related technical work for fiscal years 1998-2003, including $66.7 million for fiscal year 2003. Table 1-3 summarizes the levels of resources allocated to the 10 categories of research recommendations by this committee. The table shows the amounts of funding allocated to intramural and extramural research funding for each category. In addition, other organizations have provided funding for PM research. For example, the Electric Power Research Institute (EPRI) provided $30.1 million for the years 1998-2002, and the Health Effects Institute provided $20.9 million for that same period.[6]

The research has followed the committee's agenda through a variety of mechanisms. At EPA, research on PM was organized and placed under a manager to ensure some cohesion and exchange among investigators. EPA also engaged the extramural community of researchers through targeted cooperative agreements and requests for proposals. The committee's first report supported the funding of PM research centers that would support interdisciplinary research groups. Five centers were funded for a 5-year period in 2000. EPA has funded the Supersite program to provide intensive monitoring and characterization of particles; the data collection phase at most sites is coming to an end.

The total extent of research on PM and the resulting publications cannot be readily tracked, largely because of the research scope and the impossibility of specifying criteria to separate relevant from nonrelevant research. Together, the Health Effects Institute and EPA have maintained a database of research projects, but maintaining complete and up-to-date information has proved difficult. The approaches used in this report provide an indication of the substantial scope of the research now in progress.

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[6]Approximately half of the funding was provided by EPA and is reported in its accounting.

TABLE 1-1 The Committee's 1999 Research Investment Portfolio for Fiscal Year 2000-2010: Timing and Estimated Costs[a,b] ($ million/year in 1998 dollars) of Recommended Research on Particulate Matter

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
SOURCE, CONCENTRATION EXPOSURE											
I. Outdoor vs. human exposure	3.0										
2. Exposure to toxic PM components											
2a. Methods	1.0										
2b. Studies		4.0	4.0	4.0	4.0	4.0					
3. Emission sources	2.5	2.5	2.5	2.5							
4. Models											
4a. Source oriented[c]	4.5	4.5	4.5	4.5	4.5	4.5	4.5				
4b. Receptor oriented	1.0	1.0	1.0								
EXPOSURE–DOSE-RESPONSE RELATIONSHIP											
5. Assessment of hazardous PM components											
5a. Toxicological and clinical studies	8.0	8.0	8.0								
5b. Epidemiology	1.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0
6. Dosimetry	1.5	1.5									
7. Effects of PM and copollutants											
7a. Copollutants (toxicology)	4.0	4.0	4.0	4.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
7b. Copollutants/long term (epidemiology)	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	6.0	3.0	3.0
8. Susceptible subpopulations	3.0	3.0	3.0	3.0	3.0	3.0					
9. Toxicity mechanisms											
9a. Animal models	3.0	3.0	3.0	3.0							
9b. In vitro studies	3.0	3.0	3.0	3.0							
9c. Human clinical	3.5	3.5	3.5	3.5							

(Continued)

TABLE 1-1 *(Continued)*

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
ANALYSIS AND MEASUREMENT											
10a. Statistical analysis	1.0	1.0	1.0	1.0							
10b. Measurement error	1.5	3.0	2.0	2.0							
SUBTOTALS ($ million per year)	47.5	54.0	51.5	42.5	28.5	28.5	21.5	17.0	17.0	14.0	14.0
RESEARCH MANAGEMENT[d] (estimated at 10%)	4.8	5.4	5.2	4.3	2.9	2.9	2.2	1.7	1.7	1.4	1.4
TOTALS ($ million per year)	**52.3**	**59.4**	**56.7**	**46.8**	**31.4**	**31.4**	**23.7**	**18.7**	**18.7**	**15.4**	**15.4**

[a]The committee's rough but informed collective-judgment cost estimates for the highest-priority research activities recommended in this report. See Chapter 3 of NRC (2001) and Chapter 4 of NRC (1998) for explanations. These estimates should *not* be interpreted as a recommended total particulate-matter research budget for EPA or the nation, for reasons explained in NRC (1998).

[b]The committee provided these cost estimates as initial guidance to the development of this research investment portfolio. Available time and resources did not allow the committee to revise and update these figures since its second report (NRC 1999). Instead, the committee focused its efforts on assessing the actual scientific progress.

[c]These estimates are in addition to costs for EPA's Supersites Program and expansion of the nationwide speciation network, as well as likely expenditures by states, local agencies, and industries for source-emissions inventories and field-measurement campaigns in support of model evaluation studies (see Table 1-2).

[d]Research management includes research planning, budgeting, oversight, review, and dissemination, cumulatively estimated by the committee at 10% of project costs.

Source: NRC 1999.

TABLE 1-2 The Committee's 1999 Technical Support Estimates: Timing and Estimated Costs[a,b] ($ million/year in 1998 dollars) of Additional Technical Work Needed for Implementation of Emission-Control Programs for Airborne Particles

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
ACTIVITY											
1. Source testing by regulatory programs			5.0	5.0	5.0	5.0	5.0				
2. Compilation of interim PM emission inventory	1.0	1.0	1.0	1.0							
3. Compilation of PM emission inventory based on results of new source information							1.0	1.0	1.0		
4. Field studies in support of air quality model evaluation and testing		20.0	20.0	20.0	20.0	20.0					
TOTALS ($ MILLION PER YEAR)	1.0	21.0	26.0	26.0	25.0	25.0	6.0	1.0	1.0		

[a]Technical-support expenditures by all public and private sponsoring organizations.

[b]The committee provided these cost estimates as initial guidance to the development of this research investment portfolio. Available time and resources did not allow the committee to revise and update these figures since its second report (NRC 1999). Instead, the committee focused its efforts on assessing the actual scientific progress.

Source: NRC 1999.

TABLE 1-3 EPA Intramural and Extramural PM-Research Enacted Budgets for FY 1998-2001
($ million/year in actual dollars)[a]

NRC Committee-Recommended Research Topic	Recipient[b]	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY 2003
1. Outdoor vs. human exposure	**Total**	$6.3	$8.2	$8.1	$5.3	$1.6	$1.3
	Intramural	$4.1	$8.2	$7.6	$4.8	$1.3	$0.5
	Extramural	$2.2	$0.0	$0.5	$0.5	$0.3	$0.8
2. Exposure to toxic PM components	**Total**	**$0.5**	**$0.0**	**$0.6**	**$0.6**	**$1.7**	**$3.9**
	Intramural	$0.0	$0.0	$0.0	$0.0	$1.4	$3.2
	Extramural	$0.5	$0.0	$0.6	$0.6	$0.3	$0.7
3. Emission sources	**Total**	**$5.5**	**$7.0**	**$4.7**	**$4.5**	**$5.2**	**$6.1**
	Intramural	$3.6	$5.6	$4.2	$4.0	$4.3	$5.1
	Extramural	$1.9	$1.4	$0.5	$0.5	$0.9	$1.0
4. Air-quality models	**Total**	**$0.5**	**$0.4**	**$6.6**	**$7.2**	**$7.4**	**$9.2**
	Intramural	$0.0	$0.4	$6.0	$6.7	$5.5	$7.0
	Extramural	$0.5	$0.0	$0.6	$0.6	$1.9	$2.2
5. Assessment of hazardous PM components	**Total**	**$7.9**	**$7.9**	**$8.1**	**$6.7**	**$16.1**	**$11.1**
	Intramural	$4.1	$3.3	$4.8	$4.5	$12.1	$8.0
	Extramural	$3.8	$4.6	$3.2	$2.2	$4.1	$3.0
6. Dosimetry	**Total**	**$1.5**	**$0.6**	**$1.3**	**$1.1**	**$0.5**	**$0.4**
	Intramural	$1.0	$0.6	$0.8	$0.6	$0.4	$0.0
	Extramural	$0.4	$0.0	$0.5	$0.5	$0.2	$0.4
7. Effects of PM and copollutants	**Total**	**$2.3**	**$7.4**	**$6.4**	**$11.7**	**$7.2**	**$6.5**
	Intramural	$0.0	$2.6	$2.3	$4.7	$3.4	$4.1
	Extramural	$2.3	$4.9	$4.1	$7.0	$3.8	$2.5

8. Susceptible subpopulations	**Total**	**$8.4**	**$2.7**	**$2.9**	**$2.7**	**$4.7**	**$4.8**
	Intramural	$3.9	$2.4	$1.9	$1.7	$1.7	$2.2
	Extramural	$4.6	$0.3	$1.0	$1.0	$3.0	$2.6
9. Toxicity mechanisms	**Total**	**$5.6**	**$8.3**	**$8.2**	**$8.4**	**$7.1**	**$6.5**
	Intramural	$2.5	$2.7	$3.0	$3.6	$2.4	$2.5
	Extramural	$3.1	$5.7	$5.2	$4.8	$4.7	$4.1
10. Analysis and measurement	**Total**	**$1.6**	**$1.2**	**$1.0**	**$1.0**	**$0.8**	**$0.6**
	Intramural	$1.1	$1.2	$0.5	$0.5	$0.2	$0.1
	Extramural	$0.5	$0.0	$0.5	$0.5	$0.6	$0.5
SUBTOTAL		**$40.1**	**$43.8**	**$47.8**	**$49.3**	**$52.4**	**$50.5**
INTRAMURAL		$20.3	$27.0	$31.1	$31.1	$32.7	$32.7
EXTRAMURAL		$19.8	$16.9	$16.7	$18.2	$19.8	$17.8
Management expenses[c]		**$1.9**	**$3.6**	**$5.9**	**$1.5**	**$1.7**	**$1.7**
Working capital and operating expenses		—[d]	—[e]	—[e]	**$8.2**	**$7.0**	**$5.9**
TOTAL FOR NRC RESEARCH TOPICS		**$42.0**	**$47.3**	**$53.7**	**$59.0**	**$61.1**	**$58.1**
Implementation-Related Activity[f]							
Technical support	**Total**	**$2.9**	**$3.4**	**$3.2**	**$1.7**	**$3.0**	**$5.4**
	Intramural	$2.9	$3.4	$3.2	$1.7	$2.4	$4.7
	Extramural	$0.0	$0.0	$0.0	$0.0	$0.6	$0.6
Supersites				**$2.9**	**$2.0**	**$1.0**	**0**
Emissions characteristics, factors and controls	**Total**	**$4.0**	**$3.5**	**$1.2**	**$1.0**	**$1.3**	**$1.4**
	Intramural	$3.7	$3.2	$1.2	$1.0	$1.3	$1.4
	Extramural	$0.4	$0.4	$0.0	$0.0	$0.0	$0.0

(Continued)

TABLE 1-3 *(Continued)*

NRC Committee-Recommended Research Topic	Recipient[b]	FY 1998	FY 1999	FY 2000	FY 2001	FY 2002	FY 2003
Criteria document development	**Total Intramural**	**$1.3**	**$1.4**	**$1.4**	**$1.6**	**$1.3**	**$1.8**
SUBTOTAL		**$8.2**	**$8.3**	**$8.7**	**$6.3**	**$6.6**	**$8.6**
INTRAMURAL		$7.9	$8.0	$5.8	$4.3	$5.0	$7.9
EXTRAMURAL		$0.4	$0.4	$2.9[g]	$2.0[g]	$1.6[g]	$0.6
GRAND TOTAL		**$50.2**	**$55.6**	**$62.4**	**$65.3**	**$67.7**	**$66.7**
INTRAMURAL		$28.2	$35.0	$36.9	$35.4	$37.7	$40.6
EXTRAMURAL		$20.2	$17.3	$19.6	$20.2	$21.4	$18.4

[a]Sums of intramural and extramural costs may differ from their respective totals shown in the table because of round-off error.
[b]Extramural consists of competitive and noncompetitive awards. It includes the Science to Achieve Results (STAR) Program, PM centers, interagency agreements, cooperative agreements with universities, and supersite funding. The distribution of research efforts of PM centers to the NRC topics is based on input from each center. Intramural includes EPA personnel salaries and expenses, contracts, and cooperative agreements.
[c]Management expenses includes salaries and expenses for EPA management personnel.
[d]In FY 1998, working capital and operating expenses were tracked under a different budget element than that for PM.
[e]Working capital and operating expenses for scientific infrastructure are allocated to EPA laboratories and EPA centers based on program need. Those expenses are included under "Management expenses" for FY 1999 and FY 2000. Expenses for FY 2001-2003 have been reported explicitly.
[f]Not identified by committee as among highest priorities.
[g]Supersites.
Source: Modified from NRC 2001.

THE COMMITTEE'S APPROACH TO ITS TASK

For this report, the committee focused on the task of tracking research progress from the time of its first report. While assessing research progress to date, the committee recognizes that future research extends beyond the existence of the committee. A recommendation concerning future oversight is presented in Chapter 6.

As in prior reports, the committee did not attempt to synthesize the available information to formulate its own recommendations for a PM NAAQS. To complete its task, the committee evaluated progress on a research agenda intended to resolve key scientific uncertainties, but the outcome of the evaluation largely reflects process rather than findings. In this regard, the committee's work is distinct from that of the Clean Air Scientific Advisory Committee of EPA's SAB, which critically evaluates the criteria document and staff paper. Other NRC committees have also addressed aspects of the NAAQS process. For example, the NRC Committee on Air Quality Management in the United States prepared a report that provides scientific and technical recommendations for strengthening the nation's air quality management system, including setting, implementing, and tracking progress of the NAAQS (NRC 2004). In addition, the NRC Committee on Estimating the Health-Risk-Reduction Benefits of Proposed Air Pollution Regulations completed a report that reviews recent EPA analyses and provides recommendations for improvement of the methods used. That committee addressed issues concerned with the structure of the analysis, such as the regulatory options to evaluate, the time frame to use, and the assumptions to make about conditions with and without regulation (NRC 2002).

In approaching its task for this report, the present committee used a multipronged approach to gauge research progress. It formed working groups directed at specific research topics, and these groups organized workshops that brought together committee members and researchers to discuss the evolution of the evidence on particular topics. The committee also carried out a comparable process of discussion in developing the evaluation and synthesis approach used in this report.[7] In addition, it developed a database of peer-reviewed publications that were collected by EPA in preparing the PM criteria document (EPA 2002, 2003a). The

[7] The names listed in the preface of this report include those who participated in the committee's workshops and discussion to develop an evaluation and synthesis approach.

database served as one basis for identifying research results that have been published over the years of the committee's consideration and for assessing the extent to which important scientific uncertainties have been reduced.

The committee specifically did not evaluate the EPA-funded PM Research Centers Program, because some of its members are involved in the centers. However, the EPA Science Advisory Board (SAB) completed an evaluation of the centers in 2002 (EPASAB 2002). The SAB report concluded that the centers program has and will likely continue to produce benefits beyond those that would come from individual investigator-initiated research. It also stated that the research centers offered a number of advantages, including flexibility and adaptability in pursuing PM research, ability to foster a multidisciplinary approach from a study's inception, and ability to leverage additional resources. The SAB report also said the centers offered the possibility of undertaking research on methods development, validation, and pilot studies that are often difficult to finance by individual investigators. The SAB report concluded that the PM centers program merits continuation beyond its expiration in fiscal year 2004—through a new, fully competitive round of applications—as one part of a diverse PM research portfolio at EPA. The SAB report recommended that an overarching mechanism be developed to provide scientific advice across all the centers. It also recommended enhanced interactions among the centers and ongoing intensive air quality monitoring efforts. In addition, the report recommended a continued focus of the centers' efforts on the most critical PM research needs identified by this committee and EPA. The SAB report also emphasized the importance of ensuring that the work of the centers does not become isolated from that of other researchers within EPA and in the academic community.

ORGANIZATION OF THE REPORT

In Chapter 2, the committee discusses its approach for evaluating PM research progress. Chapter 3 provides a synthesis of PM research progress in each of the 10 topics in the research portfolio since 1997. Detailed assessments of progress for each research topic are presented in Appendix C. Chapter 4 provides an integration of progress made across the research topics, and Chapter 5 identifies key, overarching scientific challenges for the years ahead in completing the research portfolio on PM. Chapter 6 provides guidance on key management issues that the committee expects to be relevant for successfully addressing key priorities for PM research in the future, and Chapter 7 provides an overall synthesis and conclusions.

2

Committee's Approach to Evaluation Of Research Progress

INTRODUCTION

The Committee on Research Priorities for Airborne Particulate Matter was created in November 1997 with the charge of developing an agenda for research on airborne particulate matter (PM), monitoring the progress of the agenda, and evaluating the gains in scientific knowledge that resulted. The underlying purpose was to reduce uncertainties in the scientific basis for establishing the National Ambient Air Quality Standards (NAAQS) for PM. In establishing its research agenda, the committee used an integrated risk assessment framework that includes sources of air pollution and subsequent effects on health—a conceptual sequence that is integral to strategies for air pollution control (see Figure 1-1 in Chapter 1) (NRC 1998). This framework provides a basis for synthesizing available information and identifying uncertainties potentially amenable to resolution through future research. Using this strategic framework, the committee identified 10 key areas of uncertainties and corresponding topics of research need and described a research portfolio to obtain evidence directed at these uncertainties. In selecting the topics, the committee used three criteria: (1) scientific value, (2) decisionmaking value, and (3) feasibility and timing. The research agenda was set out in the committee's first report (see Chapter 1). In subsequent reports published in 1999 and 2001 (NRC 1999, 2001), the committee added three criteria relevant to evaluating the planning, management, and implementation of the agenda: (1) interaction, (2) integration, and (3) accessibility.

While the committee has been operative, the U.S. Environmental Protection Agency (EPA) has been proceeding with its mandated process to review the NAAQS for PM (Table 2-1). The timetable for EPA's review

reflects requirements of the Clean Air Act. Research complying with the committee's portfolio, which was designed to inform both current and future decisions on standards and implementation, could not be fully sequenced with this near-term review. The divergent timetables of EPA's immediate process and of the scientific research initiated after the committee's first report reflect the exigencies of implementing a major research initiative and the challenges of scheduling the pace of scientific research, which inevitably has unanticipated hurdles. Typically, at least several years are needed to move from funding to publication of even the smallest study. Large toxicological and epidemiological studies of air pollution often provide published findings 5-10 years after funding is started.

The research agenda proposed by the committee is intended to have an impact on the PM NAAQS (including its four elements: the indicator, the averaging time, the statistical form, and the level), on the subsequent implementation of that NAAQS, and on future NAAQS reviews. This chapter describes the committee's approach to evaluating research progress. Although the committee evaluates the research findings on PM on their contribution to the advancement of scientific knowledge without specific concern for EPA's application, the committee is also mindful of the impact of the research agenda and the resulting research findings on the PM NAAQS, its implementation, and future reviews.

BACKGROUND

A key step in the use of scientific evidence for policy formulation is gauging research progress resulting in reduction of uncertainty. Committees of the National Research Council (NRC) and the Institute of Medicine (IOM) are frequently asked to evaluate evidence and reach conclusions. Examples of such evaluations include the toxicity of environmental agents, the value of specific health-care practices, and approaches to disease prevention. The NRC does not give its committees a template or a rigid process for these evaluations, although some committees have had mandated approaches. Committees of EPA's Science Advisory Board often carry out similar evaluations, as do a myriad of committees of other agencies. Often the work of these committees involves hazard identification, reaching a discrete decision as to the potential of a particular agent or exposure circumstance to produce an increase in certain adverse health effects. In some cases, the evaluation may extend to a quantitative evaluation of the exposure-dose-response relationship for the agent.

TABLE 2-1 EPA's Review and Implementation Timetable for Particulate Matter Standards

Past Actions	
1971	EPA issues total suspended particles (TSP) NAAQS
1979-1987	Criteria and standards are reviewed
1987	EPA issues PM_{10} NAAQS
1994-1997	Criteria and standards are reviewed
1997	EPA issues $PM_{2.5}$ and revised PM_{10} NAAQS
1999	EPA designates areas unclassifiable, regarding attainment of NAAQS for $PM_{2.5}$
1998-2000	$PM_{2.5}$ monitors are placed nationwide
1998-2003	$PM_{2.5}$ monitoring data collected nationwide
Planned Actions	
2004[a]	EPA will complete 5-year scientific review of $PM_{2.5}$ standards, leading to possible revision
2002-2005	EPA will designate nonattainment areas for $PM_{2.5}$
2005-2008	States will submit implementation plans for meeting $PM_{2.5}$ standard.
2012-2017	States will have up to 10 years and two 1-year extensions to meet $PM_{2.5}$ standards

[a]Year may be revised by EPA.

The approaches used to evaluate an association between exposure to an agent and the occurrence of particular diseases have been variable and are still evolving. Some of the earliest attention to developing formal criteria for making such evaluations was given to evidence on cancer.

- *1964 Report of the Surgeon General on Smoking and Health:* One of the earliest evaluations of this kind was the 1964 Report of the Surgeon General on Smoking and Health (USDHEW 1964). Although this evaluation and the associated report considered multiple diseases, the primary focus—and impact—related to its conclusions on the association between smoking and lung cancer. The criteria used to evaluate the association are shown in Box 2-1.
- *International Agency for Research on Cancer (IARC):* IARC initiated a program in 1971 to evaluate the carcinogenic risk of chemicals to humans (IARC 1972). The IARC program utilizes international working

BOX 2-1 Criteria Used to Evaluate the Association Between Smoking and Lung Cancer

- Consistency of the association
- Strength of the association
- Specificity of the association
- Temporal relationship of the association
- Coherence of the association

Source: USDHW 1964.

groups of experts to conduct critical reviews and evaluate the evidence on carcinogenicity of a wide range of human exposures. The IARC panels assess the strength of the evidence that certain exposures could alter the incidence of cancer in humans. The greatest weight is given to epidemiological data but without extrapolation beyond the range of the data available. Quantitative assessments are not made. The evaluations also include consideration of the results of studies in laboratory animals. The overarching view of the IARC is that "in the absence of adequate data on humans, it is biologically plausible and prudent to regard agents and mixtures for which there is sufficient evidence of carcinogenicity in experimental animals as if they presented a carcinogenic risk to humans" (IARC 2001). Supporting data on the mechanisms by which agents may cause cancer are also considered. IARC's categorization according to the strength of evidence is presented in Box 2-2.

- *Guidelines for Carcinogen Risk Assessment (EPA 1986):* Soon after it was created, EPA was confronted with the need to develop guidelines for evaluating the carcinogenic risk of various chemicals and other agents. The guideline evolved with practice. The hazard identification facet, which addresses whether the agent has carcinogenic properties, was closely patterned after the evaluation procedure used by IARC. However, EPA, unlike IARC, could not stop with the hazard identification phase. The needs of a number of statutes required the agency to establish the carcinogenic potency (the dose-response or, most typically, the exposure-response function), which could be combined with exposure assessment to yield a

BOX 2-2 IARC's Scheme for Categorizing an Agent, Mixture, or Exposure Circumstance

Group 1: The agent (mixture) is carcinogenic to humans. The exposure circumstance entails exposures that are carcinogenic to humans.

This category is used when there is *sufficient evidence* of carcinogenicity in humans. An exception is when evidence of carcinogenicity is less than sufficient in humans but sufficient in experimental animals and when evidence is strong that the agent (mixture) acts through a relevant mechanism of carcinogenicity in exposed humans.

Group 2

This category includes agents, mixtures, and exposure circumstances for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost sufficient, as well as those for which, at the other extreme, there are no human data but there is evidence of carcinogenicity in experimental animals. Agents, mixtures, and exposure circumstances are assigned to either group 2A (probably carcinogenic to humans) or group 2B (possibly carcinogenic to humans) on the basis of epidemiological and experimental evidence of carcinogenicity and other relevant data.

2A: The agent (mixture) is probably carcinogenic to humans. The exposure circumstance entails exposures that are probably carcinogenic to humans.

This category is used when there is *limited evidence* of carcinogenicity in humans and *sufficient evidence* of carcinogenicity in experimental animals. In some cases, an agent (mixture) may be classified in this category when there is *inadequate evidence* of carcinogenicity in humans, *sufficient evidence* of carcinogenicity in experimental animals, and *strong evidence* that the carcinogenesis is mediated by a mechanism that also operates in humans. An exception is when an agent, mixture, or exposure circumstance may be classified in this category solely on the basis of *limited evidence* of carcinogenicity in humans.

2B: The agent (mixture) is possibly carcinogenic to humans. The exposure circumstance entails exposures that are possibly carcinogenic to humans.

This category is used for agents, mixtures, and exposure circumstances for which there is *limited evidence* of carcinogenicity in humans and *less than sufficient evidence* of carcinogenicity in experimental animals. It may also be used when there is *inadequate evidence* of

(Continued)

(**BOX 2-2** *Continued*)

carcinogenicity in humans, but there is *sufficient evidence* of carcinogenicity in experimental animals. In some instances, an agent, mixture, or exposure circumstance may be placed in this group when there is *inadequate evidence* of carcinogenicity in humans but *limited evidence* of carcinogenicity in experimental animals together with supporting evidence from other relevant data.

Group 3: The agent (mixture or exposure circumstance) is not classifiable as to its carcinogenicity in humans.

This category is used most commonly for agents, mixtures, and exposure circumstances for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals. An exception is when agents (mixtures) that have *inadequate evidence* of carcinogenicity in humans but *sufficient evidence* in experimental animals are placed in this category because there is *strong evidence* that the mechanism of carcinogenicity in experimental animals does not operate in humans. Agents, mixtures, and exposure circumstances that do not fall into any other group are also placed in this category.

Group 4: The agent (mixture) is probably not carcinogenic to humans.

This category is used for agents or mixtures for which evidence suggests a *lack* of carcinogenicity in humans and experimental animals. In some instances, agents or mixtures may be classified in this group when evidence of carcinogenicity is *inadequate* in humans, but evidence that is consistently and strongly supported by a broad range of other relevant data suggests a *lack* of carcinogenicity in experimental animals.

Source: IARC 2001.

quantitative assessment of risk. The controversy surrounding the entire carcinogenic risk assessment process led the agency to request the assistance of the NRC, the results of which are described below.

Other committees of the NRC and IOM have also identified systems for evidence evaluation and synthesis to inform policy processes. Several key and relevant frameworks are reviewed below as background.

- *Risk Assessment in the Federal Government: Managing the Process (NRC 1983):* The goal of this report was to develop a process in

which scientific evidence could be organized, judged, and synthesized in a sound and reproducible manner; thereby, ensuring the integrity of the evidence used to inform risk management policy. That committee examined preexisting inference guidelines to identify relevant lessons applicable to risk assessment, but the focus of the report was on systematic evaluation of scientific evidence for policy determinations. Types of evidence considered by that committee included epidemiological, animal bioassay, and experimental studies along with comparisons of molecular structure. Like IARC (1972), the NRC committee viewed epidemiological studies as the most convincing evidence of risk, but animal bioassays were recognized as more commonly available and useful, as long as their results could be extrapolated to humans. All types of studies were evaluated for their strengths and weaknesses and for their contributions to risk assessment processes. Specific questions that should be used to evaluate the literature were listed for each of the four steps of the proposed risk assessment paradigm (NRC 1983, pp. 29-33). That committee concluded that risk assessment guidelines should enable the evaluation of data quality, be flexible but include default statements, allow for the incorporation of new evidence as it emerges, and result in a judgment of the overall strength of the evidence.

• *Science and Judgment in Risk Assessment (NRC 1994):* Throughout the 1980s, risk assessment procedures, especially those used for carcinogenic risks, generated substantial debate. In response to this controversy, the Clean Air Act Amendments of 1990 directed the administrator of EPA to engage the NRC in a review of the methods that EPA used to estimate toxicological risk. The EPA administrator and the NRC proceeded as directed with the formation of a committee whose evaluation and findings are documented in its report. The committee largely endorsed the recommendations of the 1983 NRC report discussed above (NRC 1994). The report identified and addressed six themes that the committee viewed as cutting across the various steps of risk assessment and arising from criticisms of each step. These themes are default options (the generic approaches taken in the absence of specific scientific knowledge), data needs, validation, uncertainty, variability, and aggregation. Although all the themes are relevant to this report, it is appropriate to make special note of two themes:

— *Uncertainty:* Has EPA taken sufficient account of the need to consider, describe, and make decisions in light of the inevitable uncertainty in risk assessment?

— *Variability:* Has EPA sufficiently considered the extensive variation among individuals in their exposures to toxic substances and in their susceptibility to cancer and other health effects?

In this report, considerable attention is given to both uncertainty and variability.

• *Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam (IOM 1994):* The IOM Veterans and Agent Orange Committee was charged with evaluating the strength of the scientific evidence for associations between herbicides and a list of adverse health outcomes but not with judging the causal nature of associations found. Although the ultimate use of its work was for processing compensatory claims, the committee was not responsible for linking the results of its evaluation with policy decisions. Extensive consideration was given in its report to the rationale and structure needed to complete the task. The committee defined three key questions, identified the types of evidence needed to address them, considered both quantitative and qualitative analytical methods, developed criteria to assess the overall strength of the evidence, and defined four categories to summarize its integrated interpretation of the evidence for each health outcome.

Even though the committee built on Hill's (1971) criteria for causality and IARC's (1977) categories of association, it began judging the evidence from a point of neutrality: integration of the evidence moved the committee's judgment either in a specific direction (for or against an association's existence) or kept it neutral. Furthermore, quantitative assessments were not sufficient alone to judge the evidence, but results consistent with the qualitative analysis could strengthen the rationale for the final categorization. Key elements of the committee's process are summarized in Box 2-3.

• *Multiple Immunizations and Immune Dysfunction (IOM 2002):* The Immunization Safety Review Committee systematically reviews the scientific evidence for a series of selected vaccine safety concerns, assesses the societal importance of the issues, and provides recommendations for further action (IOM 2002). In a report on multiple immunizations and immune dysfunction, the committee articulated its study process and its framework to assess the scientific evidence of vaccines and adverse health outcomes—for example, the hypothesis that multiple immunizations can harm the developing immune system. The committee adopted the framework for causality developed by previous IOM committees (1991, 1994) (Table 2-2). However, public confusion about the term "biological

BOX 2-3 Categories of Causal Conclusions

- No evidence
- Evidence is inadequate to accept or reject a causal relationship
- Evidence favors rejection of a causal relationship
- Evidence favors acceptance of a causal relationship
- Evidence establishes a causal relationship

Sources: IOM 1991, 1994.

plausibility" indicated that further clarification of its evaluative framework was needed. The committee recognized that Hill's original intent in regard to the biological plausibility criterion in judging epidemiological causality

TABLE 2-2 Evaluation of the Strength of the Evidence on Agent Orange (Are herbicides statistically associated with the health outcome?)

Types of evidence	o Animal models o Observational studies o Exposure studies
Criteria for strength of the evidence	o Quantitative ▪ Resolution ▪ Uncertainty and confidence o Qualitative ▪ Comprehensiveness ▪ Neutrality ▪ Judgment
Categories of association	o Sufficient evidence of an association o Limited, suggestive evidence of an association o Inadequate, insufficient evidence to determine whether an association exists o Limited, suggestive evidence of no association

Source: IOM 1994.

was to have a basis to judge the consistency of existing biological knowledge with epidemiological findings in a single study (Hill 1971). However, the goal of the committee's comprehensive review of the literature on biological mechanisms was to determine whether a mechanism had been hypothesized only or whether there was support for a mechanism in experimental, animal, or human research. Consequently, the committee separated its evaluation of the literature on biological mechanisms from its judgment of the evidence for causality in population-based studies. The committee then combined the determination about biological mechanisms with its assessment of clinical and epidemiological data to judge whether scientific evidence supported causal relationships between multiple immunizations and immune dysfunctions. Figure 2-1 shows the committee's approach, which proceeds from a synthesis of the evidence to conclusions based on that synthesis to recommendations for public health responses. The committee was responsible for (1) assessing both the scientific evidence and the societal importance of the issue to develop its conclusions and (2) presenting policy, research, and communication recommendations based on its conclusions. According to its charge, the committee was permitted to recommend that immunization policy be reviewed or analyzed but could not recommend changes to immunization policies.

The present committee found applicable concepts and approaches in the work of these and other NRC committees. In proposing its integrated risk assessment framework, this committee drew on the formalization of risk assessment that emerged with the 1983 NRC report *Risk Assessment in the Federal Government: Managing the Process* and was rearticulated in *Science and Judgment in Risk Assessment* (NRC 1994) and the need to identify points of uncertainty requiring default assumptions in carrying out a quantitative risk assessment emphasized in the 1994 NRC report. The committee also found the dual and parallel synthesis approach for animal and human data of the Immunization Safety Review Committee (IOM 2002) to be a valuable model. However, the present committee faced the task of evaluating progress on its research agenda and not with evidence review for the purpose of reaching a causal conclusion. In addition, present policies are largely based on evidence related to the quantitative risks of air pollution rather than on the determination that a hazard exists—the emphasis of most reports reviewed above.

EPA has a process for evaluating evidence on pollutants for which NAAQS are set (Figure 2-2). The agency faces the challenge of periodic evidence evaluation as the criteria document and staff paper are prepared for the criteria pollutants for which NAAQS are set. The NAAQS process includes three key steps. The first step is preparation of a criteria document,

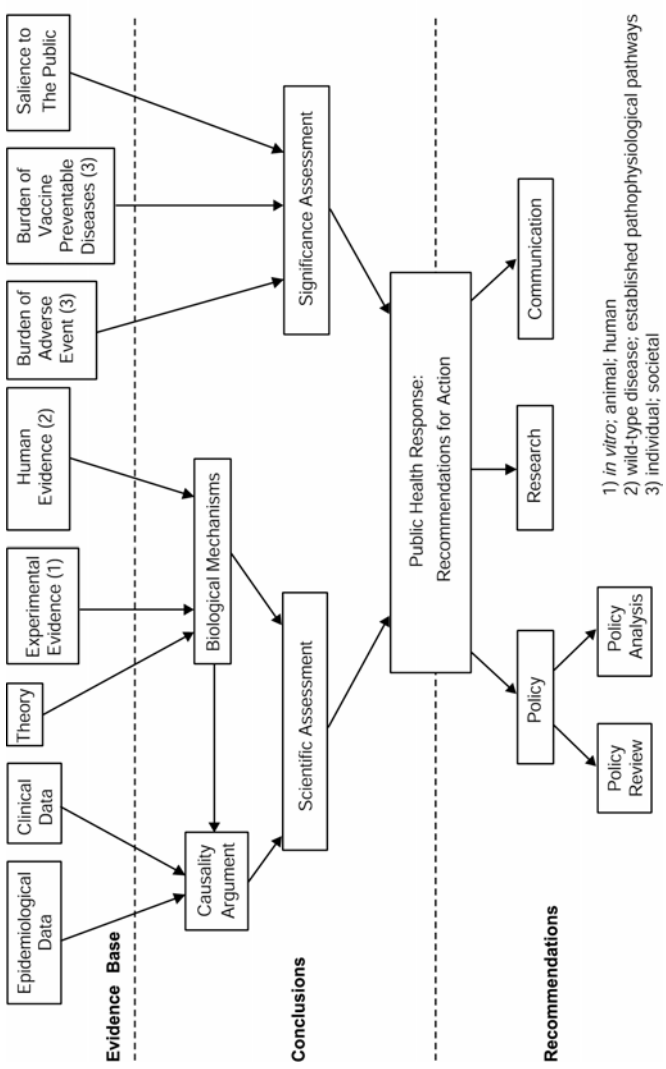

FIGURE 2-1 Charge to the Immunization Safety Review Committee. Source: IOM 2002.

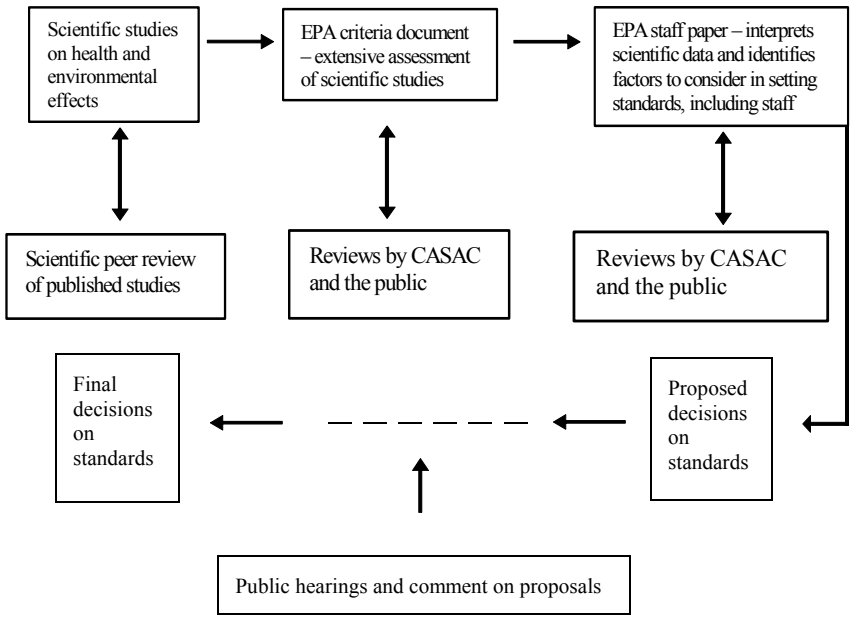

FIGURE 2-2 Schematic of EPA's evaluation of evidence for setting standards for criteria pollutants. A separate process (not shown here) is used to design and implement control strategies. Abbreviation: CASAC, Clean Air Scientific Advisory Committee.

which catalogs and summarizes all the available peer-reviewed and published information on the criteria pollutant, such as PM, under consideration. The criteria document is prepared by EPA's Office of Research and Development with major input from scientists outside the agency. No formal methodology is in place for this summarization, nor for moving from the criteria document to the staff paper, the second step.

The second step is preparation of a staff position paper, which summarizes the literature that specifically informs decisions on the four elements of a NAAQS. This document, prepared by EPA's Office of Air Quality Planning and Standards, concludes with recommendations on the range of options for the four elements of the NAAQS. The third step is EPA's promulgation (final decision) of the proposed NAAQS, including each of the four elements.

EPA's Clean Air Scientific Advisory Committee (CASAC) reviews the criteria document and the staff paper, and when CASAC considers that

the documents provide a scientifically adequate review of the literature, a closure letter is sent to the EPA administrator. CASAC has the authority to review the proposed NAAQS, but has not always done so. Following establishment of the NAAQS, states are required to develop implementation plans for control strategies to achieve the NAAQS.

In its consideration of the above and other approaches, the committee did not find a specific model that could be directly transferred to its review and particularly to its evaluation of the degree of change in uncertainty. It did find useful elements in many of the processes elaborated by others. Additionally, any synthesis process adopted by the committee would need to be tailored to reflect the specifics of characterizing the association of PM with risk to human health. Among the challenging aspects of the task are the multiplicity of sources of PM, the complexity of airborne PM, the strong possibility that multiple mechanisms are relevant to disease causation, and the lack of specificity for the health outcomes of concern.

The committee noted that the evidence evaluation systems that it had reviewed did not cover a number of large scientific issues relevant to the review and implementation of a NAAQS. The evidence evaluation systems reviewed focused on classifying causality of associations between exposure to an agent and an increase in the probability of adverse health outcome in a population, thus, identifying a hazard. In both the setting of the NAAQS for PM and in the implementation of control strategies to achieve the NAAQS, there is a need to move beyond the issue of whether PM or some other pollutant is hazardous and consider the potency of PM or the other pollutant. Knowledge of exposure of a population and the potency of the pollutant are required to estimate the population risk.

In the setting of the NAAQS, EPA is required to set the standard at a level that provides an adequate margin of safety for protecting the public, including sensitive populations, from adverse health effects. Although EPA cannot consider costs or benefits in setting the NAAQS, it used risk assessments that quantify changes in health outcomes at various pollutant concentrations to inform decisions on the NAAQS. In the implementation phase, cost-benefit information can be used to select control options. Thus, information on the potency and other aspects of exposure-dose-response relationships is another consideration in evaluating research progress on PM. Some examples include characterization of the toxicity-determining characteristics of particles and quantifying, with sufficient certainty, exposure-dose-response relationships with outcome measures. The discrete characterization of associations as causal or not causal does not address these evidence synthesis examples.

THE COMMITTEE'S EVALUATIVE APPROACH

The committee accepts the premise that the ultimate goal of research on air pollution, as for any other environmental hazard, is to improve public health and secondarily to protect public welfare (Figure 2-3). Figure 2-3 sets out a sequence that begins with a research agenda that responds to major information uncertainty and ends with demonstrated benefit to public health. For air pollution, this sequence may well span years or decades, given the timing of research and the schedule for regulation and implementation. Although this framework is simplistic, the committee found it to be useful for identifying evaluation indicators on differing time scales. For this report, the committee focuses on the more proximal indicators of progress on the research agenda and the consequences of this work: funding, research initiated, publications, and extent of incorporation of findings of new research motivated by the committee's agenda into the criteria document and staff paper.

Even within the life span of the committee, substantial research has been funded, initiated, and published. EPA's fourth external review draft of the criteria document for PM, for example, includes 289 references in its exposure chapter, 294 references in its toxicology chapter, and 431 references in its epidemiology chapter (EPA 2003a). This research has been carried out in diverse venues, including EPA's intramural and extramural research activities as well as academic and other research institutions funded by the National Institutes of Health and other organizations, such as the Electric Power Research Institute (EPRI) and the Health Effects Institute (HEI), with interest in the health effects of air pollution. The committee's research portfolio was directed primarily toward EPA, but it also considered PM-related research conducted, funded, or planned by other agencies and organizations in the United States and abroad. Therefore, in evaluating available research, the committee considered relevant U.S. research supported by EPA as well as that supported by other sources and key research outside the United States initiated in the proper timeframe. For each topic, the committee surveyed

- *Expenditure*s by EPA and by other agencies to the extent possible. For EPA, expenditures are stratified as intramural or extramural.
- *Research Projects* initiated by EPA, other agencies, and the research community in general.
- *Publications* in the peer-reviewed literature during the time that the committee's reports were expected to have had impact.

The published findings represent another point for evaluation, as they reduce the points of uncertainty that motivated their conduct. The committee is aware of publications on several of the 10 topics that reflect studies implemented as a consequence of the committee's reports. For these studies, the committee subjectively gauged the extent to which uncertainty had been reduced. The committee also assessed the studies related to each topic quantitatively and qualitatively: (1) Have relevant studies been published? (2) How many? (3) Are the findings consistent? (4) Is sufficient information available to explain any substantial discrepancies in the findings? and (5) To what extent has uncertainty been reduced? The committee used these five criteria as a yardstick within each topic to gauge reduction of uncertainty, in addition to its overall judgment of the degree of reduction in uncertainty (see Chapter 3).

To facilitate this aspect of its evaluation, the committee carried out workshops during the year before this report was prepared, bringing together expert panels in the general areas corresponding to its research topics: exposure assessment (topics 1 and 2), sources and models (topics 3 and 4), and epidemiology and toxicology (topics 5, 6, 7, 8, 9, and 10). In these workshops, researchers and others who were not committee members were asked to provide an evaluation of progress on specific areas of research. In addition, a workshop was held to consider methodologies for evaluation of research advances and reduction of uncertainty. Discussion at that workshop served as a basis for this chapter.

For this report, the committee also assessed the extent to which research initiated at its recommendation has been considered in the criteria document and staff paper. Given the limited time since the committee's first report (approximately 6 years), this criterion would be expected to have limited sensitivity except perhaps for topic 1 (exposure assessment) and topic 10 (methods). Other more-distal criteria shown in Figure 2-3 cannot be expected to be informative at present but should be monitored and included in any future reports on research progress related to PM.

Research implementation, management, and *interactions* were also considered by the committee with respect to enhancing research progress by using the three criteria (accessibility, interaction, and integration). These criteria will be applied in general, across the range of research (see Chapters 4, 5, and 6).

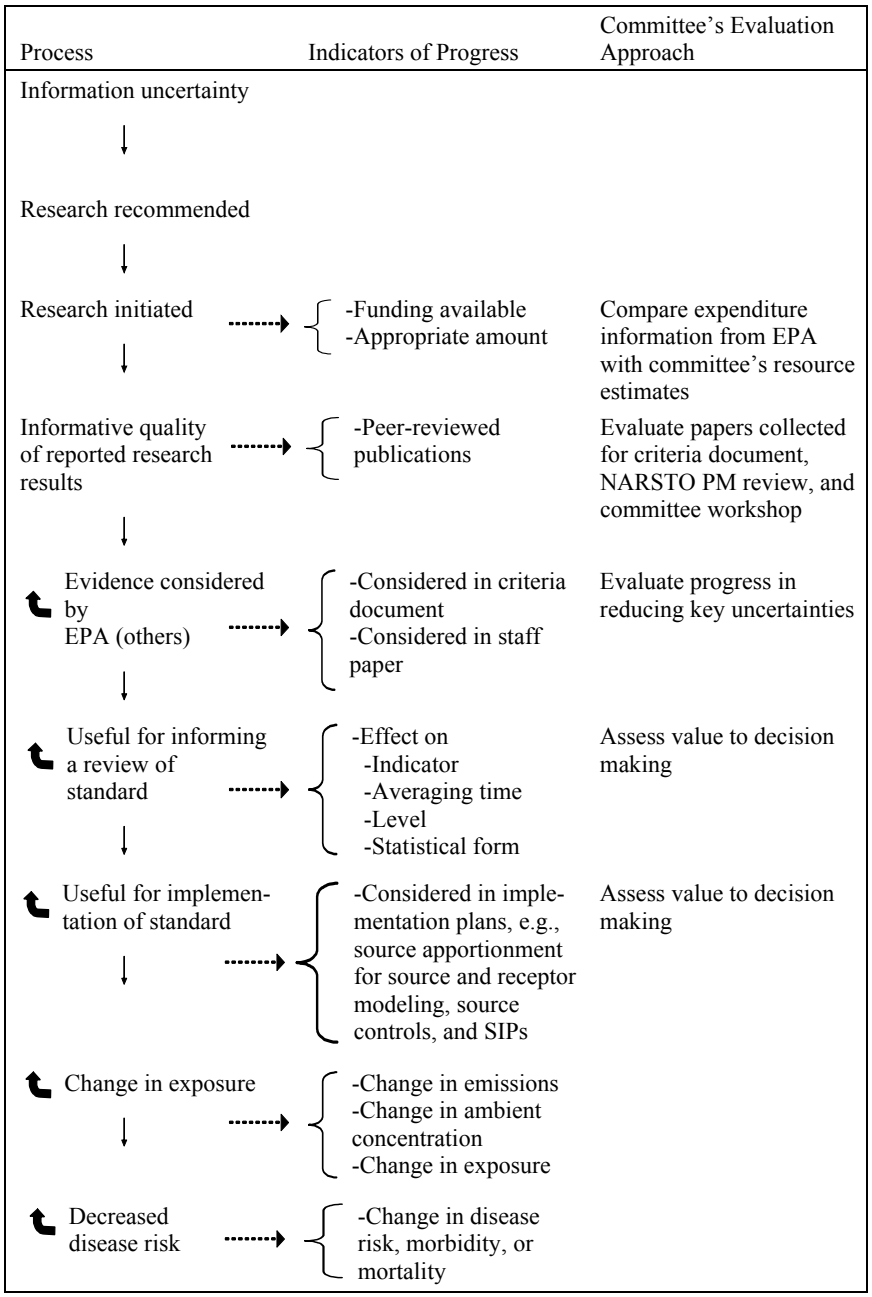

FIGURE 2-3 Schematic representation of process for reducing disease risk through research.

CONSIDERATIONS IN INTERPRETING RESEARCH PROGRESS ON PARTICULATE MATTER

The committee notes that reduction of uncertainty, the overall goal of its research agenda, is never complete. EPA by the mandate of the Clean Air Act with regard to the NAAQS is inevitably making decisions in a background of scientific uncertainty. As it seeks to satisfy the requirements of the Clean Air Act to set standards to protect public health with an "adequate margin of safety," its decisionmaking inherently involves PM concentrations at which effects do not occur with known probability or certainty. Additionally, the health effects of PM and their mitigation are a topic of evident complexity. Often, resolution of one uncertainty only highlights other uncertainties that still cloud decisionmaking. Furthermore, as the methods of scientific inquiry deepen, uncertainties that have seemingly been resolved may again become a focus of research as new methods facilitate resolution at a more profound level of inquiry.

Although the committee addressed a broad range of research topics in evaluating scientific process, it did not choose to judge one of its initial recommendations, the establishment of centers for research on PM. The EPA Science Advisory Board (SAB) completed an evaluation of the centers in 2002 (EPASAB 2002).

3

Synthesis of Research Progress On Particulate Matter

INTRODUCTION

The committee's first report set out the sources-to-health-effects framework (see Figure 1-1 in Chapter 1) that has been integral to the development of the particulate matter (PM) research portfolio and to tracking progress with the agenda (NRC 1998). The framework has proved useful for identifying needed elements of the research portfolio and for addressing integration of research findings in support of implementation of evidence-based control strategies. In this chapter, the committee reviews progress on each of the 10 original research topics (see Box 1-1 in Chapter 1), summarizing the gains in scientific knowledge for each from 1998 until the middle of 2002 with some additional updating over the next year as this report was written and particularly relevant contributions were made. The committee also considered the remaining uncertainties, and what remains to be done. In addition, the committee assessed the studies related to each topic quantitatively and qualitatively according to the five criteria listed in Chapter 2. The committee's more extended evaluations of the progress are provided in Appendix C. The focus of the committee's evaluation has been research funded by the U.S. Environmental Protection Agency (EPA) with additional consideration of research funded by other organizations in the United States and abroad.

RESEARCH TOPIC 1. OUTDOOR MEASURES VERSUS ACTUAL HUMAN EXPOSURES

What are the quantitative relationships between concentrations of particulate matter and gaseous copollutants measured at stationary outdoor air monitoring sites and the contributions of these concentrations to actual personal exposures, especially for potentially susceptible subpopulations and individuals?

Introduction

Compliance with the National Ambient Air Quality Standards (NAAQS) for PM is ascertained by measuring ambient concentrations of PM at monitoring sites. With regard to the health effects of air pollution, the risks depend on personal exposure—that is, the exposures received by people in the various specific places, conceptualized as microenvironments, where they spend time. Total personal exposure represents the time-weighted average of particle concentrations in the microenvironments where people spend their time. Exposures to particles generated by outdoor sources take place not only outside but also in indoor environments where the particles penetrate. Indoor particle sources, such as cigarette smoking, insects, molds, and cooking, may thus contribute substantially to total personal exposure to particles. Research carried out in regard to this topic addresses the relationship of monitoring data for ambient air with personal exposures to PM and gaseous copollutants. Data on this relationship are needed not only for healthy people but also for those persons who are particularly susceptible to air pollution and at greatest risk for experiencing adverse effects. Such persons are referred to collectively as a "susceptible subpopulation" and are further addressed under topic 8 later in this chapter.

What Has Been Learned?

Research findings on topic 1 are relevant to interpreting the findings of the epidemiological studies of PM and to furthering the understanding of the relevance of monitored ambient concentrations for public health protection. Before 1997, the majority of time-series studies of morbidity and mortality associated with PM had relied on ambient air measurements taken for regulatory and tracking purposes. In using these measurement data in

the time-series studies, the researchers assumed that outdoor particle concentrations serve as a valid surrogate of personal exposures to ambient particles. Previous findings from monitoring studies had suggested that personal exposures differ from ambient concentrations because of particle sources in key indoor microenvironments (Dockery and Spengler 1981; Ozkaynak et al. 1993; Ozkaynak et al. 1996). In addition, most of these investigations found weak associations, often not statistically significant, between personal exposure and ambient concentrations when assessed cross-sectionally (at different locations for different people). However, these conclusions were based on a relatively small number of studies, which were originally designed to determine population exposure distributions rather than to examine the degree of association between personal exposures and ambient concentrations. For interpreting the time-series studies of air pollution and health, an understanding of the pattern of association between ambient concentrations and personal exposures over time was needed.

To address this knowledge gap, the committee recommended that longitudinal panel studies of personal exposure to PM be conducted (NRC 1998). In such studies, particle and gaseous copollutant exposures of groups of individuals would be measured at successive points in time to examine the relationship between personal exposures and the corresponding ambient concentrations. Further, these studies would attempt to identify factors influencing the observed relationships. The recommended exposure assessment studies would include not only healthy individuals but also emphasize individuals susceptible to the effects of particle exposures, including persons with chronic obstruction pulmonary disease (COPD), cardiovascular disease, and asthma, as well as children and older adults. As a result of the committee's recommendations, a large number of particle exposure studies were conducted in several cities in the United States with different climatic conditions and air pollution mixtures. Studies were also conducted in Europe and South America. Below we summarize the major findings that have emerged from either the initial or the completed analyses of the collected data.

Relationship Between Personal Exposures and Ambient Concentrations

Results from the recent panel studies support the hypothesis that ambient $PM_{2.5}$ concentrations are significant predictors of corresponding personal exposures, over time, for the investigated cohorts (Ebelt et al.

2000; Evans et al. 2000; Rojas-Bracho et al. 2000; Sarnat et al. 2000, 2001; Williams et al. 2000a,b; Rodes et al. 2001). Stronger associations were observed as the number of repeated measures per individual increased from a few up to 15 days and were substantially higher than those determined when including all panel data (cross-sectional analysis). Most of the panel studies found little spatial variability of ambient $PM_{2.5}$, thus suggesting that spatial variation is not a strong determinant of the level of correlation within the areas studied. Collectively, the results from the panel studies, performed on several hundred individuals across various cities and different seasons, showed that there were varying degrees of association between personal exposures and ambient concentrations for the measured individuals, with almost half of the associations being non significant. For those individuals and for $PM_{2.5}$, the correlation coefficients were in the range of 0.4 to 0.9.

Impact of Nonambient Sources

Near-real-time $PM_{2.5}$ indoor measurements have underlined the importance of nearby sources (such as cooking stoves) that are within the various microenvironments in which people spend their time (referred to as microenvironmental sources) (Abt et al. 2000; Howard-Reed et al. 2000; Long et al. 2000; Rea et al. 2001; Vette et al. 2001). However, exposures in specific microenvironments have not been shown to have a strong effect on the relationship of personal exposures with ambient concentrations over time. This generally weak relationship may be explained by the fact that indoor source uses and associated emissions are intermittent and, when averaged over 24-hr sampling periods, contribute to a small fraction of the total $PM_{2.5}$ exposure variability for a particular person over time. This may not be true for certain exposure situations, for instance, when ambient concentrations measured at stationary outdoor air-monitoring sites are low and individuals are exposed to strong sources in specific microenvironments (such as cigarette smoking, wood burning, and motor vehicle traffic).

Impact of Ambient Concentrations on Personal Exposures

The fraction of ambient particles that penetrates indoors varies considerably (from approximately 0.3 to 1.0), and it increases with the home air-exchange rate (Sarnat et al. 2002). Air conditioning and patterns of home

activities, such as opening windows and doors, which influence home air-exchange rates, are factors determining the rate of particle penetration from outdoor into indoor air. Consequently, individuals residing in homes with higher air-exchange rates tend to be exposed to higher fractions of ambient particles, and their personal exposures tend to be more strongly associated with ambient concentrations (Sarnat et al. 2002; Liu et al. 2003; Wallace et al. 2002). In addition, fine-particle penetration from outdoor air into indoor air depends on particle size; the penetration of the accumulation mode (aerodynamic diameter, approximately $0.3 < d_a < 1$ μm) is higher than that of the ultrafine mode and larger particles (Long et al. 2001; Vette at al. 2001). Until recently, the variability in a person in particle exposures was thought to be primarily from microenvironmental sources. However, there is now strong evidence that a great fraction of this variability is due to the varying impact of ambient sources on the indoor environments and therefore on personal exposures (Landis et al. 2001; Williams et al. 2002). Sulfate is associated mostly with outdoor particle sources and has been used to determine the contributions of outdoor and indoor sources to personal exposures (Wilson and Suh 1997; Ebelt et al. 2000; Oglesby et al. 2000; Sarnat et al. 2000; Landis et al. 2001). Sulfate is a suitable tracer for the accumulation mode; however, it may overestimate the penetration of ambient ultrafine and coarse particles indoors. As suggested by both fine-particle sulfate and mass measurements, the fraction of ambient particles to which populations are exposed may depend on climatic conditions and home characteristics among other factors and may vary from 0.2 to 0.9 (Brown et al. 2003; Rodes et al. 2001).

Cohort Effect

When the longitudinal exposure studies were initiated, it was hypothesized that personal exposures may differ for different groups within a population because of time-activity differences among the investigated cohorts. To date, available evidence has not indicated intergroup difference, as hypothesized. Findings in a panel study of nonsmoking hypertensive African-Americans were compared with those in a multiracial cohort of individuals with implanted cardiac defibrillators (Wallace et al, unpublished material, 2003). Time-activity patterns exhibited considerable intracohort variability; however, statistically significant intercohort differences in $PM_{2.5}$ exposures were not found. In another study, personal $PM_{2.5}$ exposures were measured for healthy nonsmoking senior citizens, school children, and

individuals with COPD in two cities (Brown et al. 2003). No significant differences among the groups were found in the relationship between personal exposures and ambient concentrations.

Exposures to Gaseous Copollutants

In several cohort studies, simultaneous 24-hr personal $PM_{2.5}$, ozone (O_3), sulfur dioxide (SO_2) and nitrogen dioxide (NO_2) exposures and corresponding ambient concentrations were measured using a personal multipollutant sampler. The findings of these studies suggested that $PM_{2.5}$ personal exposures and ambient concentrations were correlated over time, and personal exposures to O_3, SO_2, and NO_2 were not correlated with their respective ambient concentrations (Sarnat et al. 2001). In contrast, $PM_{2.5}$ personal exposures were also correlated with O_3 and NO_2 ambient concentrations. Similar findings in other locations would imply that using ambient gaseous concentrations in multipollutant health-effects models along with $PM_{2.5}$ might not be appropriate, because the ambient gaseous and $PM_{2.5}$ concentrations are serving as surrogates for $PM_{2.5}$ exposures (Williams et al. 2000c; Vette et al. 2002). No results are available, however, for carbon monoxide (CO) because short-term or continuous personal exposure measures have not been made for this pollutant gas.

What Remains To Be Done?

Substantial progress has been made in answering the research questions related to topic 1. The committee was able to identify a large number of studies conducted in various locations, such as Baltimore, Boston, and Research Triangle Park, NC, that had been initiated following the first report. For most, the field work is now complete, and results are being published in the peer-reviewed literature. Advances have been made in personal monitoring, and data can be feasibly collected, not only from healthy adults but also from children and persons with chronic heart and lung diseases. The monitoring studies provide the important and generally consistent finding that ambient particle concentrations are a key determinant of the longitudinal variation in personal exposure to particles for those groups studied to date. This finding is critical for interpreting the time-series analyses as well as other epidemiological studies of particles and health.

Although substantial data have been collected, they are not sufficient to develop a national perspective on the relationship between ambient PM

concentrations and personal exposure, because data are lacking for fully representative persons and locations. Also, there is still little information about the exposures of susceptible individuals to particles and other air pollutants. Further studies are needed, particularly on those persons at the highest risk for illness or death.

RESEARCH TOPIC 2. EXPOSURES OF SUSCEPTIBLE SUBPOPULATIONS TO TOXIC PARTICULATE MATTER COMPONENTS

What are the exposures to biologically important constituents and specific characteristics of particulate matter that cause responses in potentially susceptible subpopulations and the general population?

Introduction

Research topic 2 extends research topic 1, shifting the emphasis on exposures to specific types of particles that have been found to be associated with greater risk for health effects. In the committee's portfolio, research related to topic 2 would be implemented only after the work under topic 5 sufficiently advanced understanding of particle characteristics that determine their toxicity, as discussed below.

What Has Been Learned?

Before 1997, very little information existed on particle exposures and chemical composition and size characteristics of the particles. Therefore, the database on exposures to particles in relation to the characteristics of the particles, particularly those considered to convey toxicity, needed to be expanded. The committee highlighted the need to characterize the physical and chemical properties of exposure particles for both the general public and susceptible subpopulations. Specifically, population-based field studies would provide information on the distribution and intensity of exposure for defined components and specific size fractions. In addition, longitudinal studies would investigate the relationship between personal exposures and ambient concentrations for specific components and particle size fractions. Toward that end, the committee suggested that state-of-the-art personal exposure measurement methods be developed and implemented. Subse-

quently, comprehensive and cost-effective field studies would be designed to determine population exposures, building on the results from the longitudinal panel studies (topic 1).

To date, the research conducted on exposures to the toxic components of PM (such as metals and organics) in a limited number of exposure studies focused on methods development and applications of speciation techniques. Those efforts will be useful in the initial chemical characterizations of exposure particles and in the design of future exposure studies. However, the techniques can only be fully implemented in exposure studies after ongoing and future toxicological studies identify components of biological relevance. Specific progress is detailed below.

Personal sampling devices have been developed and field tested. These methods make it possible to obtain information on personal exposures to different particle fractions and their components. More specifically, new methods have been developed for PM_{10} and $PM_{2.5}$, ionic species, elements, elemental and organic carbon, and organic compounds (Demokritou et al. 2002). In addition, new personal sampling devices allow for the simultaneous collection of gaseous copollutants, $PM_{2.5}$ and PM_{10}, and particle composition (Chang et al. 1999; Demokritou et al. 2001). The development of new sampling and analysis protocols in conjunction with the use of more sensitive analytical techniques makes it possible to improve measurement precision and accuracy. One of these advances is a decrease in the flow rates of air into sampling devices, making smaller personal sampling devices possible.

Real-time personal exposure measurements of fine mass and ultrafine particles have been conducted and have demonstrated the importance of nearby (microenvironmental) sources in determining total personal exposures (Fischer et al. 2000). These measurements will be critical to efforts in identifying sources that contribute to personal exposures and link exposures to specific activities or events. Furthermore, state-of-the-art exposure health effects studies have conducted simultaneous real-time personal exposure and biological monitoring (Liao et al. 1999; Howard-Reed at al. 2000). This was done to link magnitude and duration of exposures to biologically relevant events. Specifically, studies have examined the relationships between real-time fine particles and adverse cardiac functions.

A limited number of studies have conducted measurements of personal exposures to various particulate constituents, including sulfate, nitrate, ammonium, elemental and organic carbon, and elements (Ebelt et al. 2000; Sarnat et al 2000; Williams et al. 2000a,b). Such studies enable the investigation of relationships between personal exposures to specific particle constituents and the corresponding ambient concentrations.

What Remains To Be Done?

Although monitoring methods are being developed for the goals of topic 2, the uncertainties associated with the topic remain largely unaddressed. The committee's sequence of research calls for more substantial advances under topic 5 before fully implementing topic 2. Exposure studies will be necessary for components of biological relevance. These investigations should examine relationships among personal exposures to particle components of biological relevance and corresponding ambient concentrations for susceptible subpopulations and the general public. Some of these studies should characterize exposure distributions for a variety of microenvironments, such as work, school, and transportation environments. The data from EPA's Speciation Trends Network may provide a useful starting point for designing exposure studies that will give a national perspective and explore geographic differences in patterns of exposure.

RESEARCH TOPIC 3. CHARACTERIZATION OF EMISSION SOURCES

What are the size distribution, chemical composition, and mass emission rates of particulate matter emitted from the collection of primary-particle sources in the United States, and what are the emissions of reactive gases that lead to secondary-particle formation through atmospheric chemical reactions?

Introduction

A large variety of anthropogenic and natural emission sources contribute to airborne PM (see Box 3-1 and Table 3-1). Emissions from these sources need to be characterized for several purposes, including health effects research and implementation of PM standards. The development of laboratory exposures that assess the toxicity of emissions from specific sources (topic 5) requires knowledge of the characteristics of emitted and secondary particles. Emissions from critical sources need to be well-characterized for confidence to be placed in the source- and receptor-oriented air quality models (topic 4), particularly as they are used to develop emission-control strategies for achieving the PM NAAQS. In its second report (NRC 1999), the committee noted that traditional emission inventories have

BOX 3-1 Emissions and Emission Inventories

Particulate matter is produced by a diverse array of emission sources. Some emissions emerge directly in the liquid or solid phase, as "primary" particles, such as combustion nuclei or mechanically generated dusts. Additional particulate species, such as sulfuric acid and its ammonium salts, ammonium nitrate, and a diverse array of organic compounds, are produced in the atmosphere by reactions that involve precursors emitted as gases. This "secondary" PM can condense on existing particles, form new particles through homogeneous nucleation, or be left as the residue of evaporated cloud droplets.

An emissions inventory is an accounting of emissions. It is typically based on a census of source types (for example, number of automobiles and powerplants), their activity (number of kilometers traveled, British thermal units generated from burning fuel), and average emission factors (grams of emissions per kilometer, kilograms of emissions per million British thermal units). Emissions from a class of sources are expressed as a rate (kilogram per day) that are typically estimated as the product of source activity (for example, kilometer per day for motor vehicles or British thermal units per day for boilers) and an emissions factor (for example, kilogram per kilometer or kilogram per British thermal unit). All emission inventories involve uncertainties arising from the use of a single emissions factor to characterize all the individual elements in a broad class of sources.

Inventories of primary-particle emissions present a number of special challenges. One is that direct comparisons with observed ambient concentrations are confounded by the possible contributions of secondary material. For example, particulate ratios of organic carbon to elemental carbon may be higher in ambient observations than in emission inventories because either (1) the inventories underestimate important sources of primary organic particles (such as oil-burning vehicles or vegetative combustion), or (2) the ambient particles contain secondary organics formed in the atmosphere from hydrocarbons (such as biogenics) emitted as gases and thus not covered by the particle inventory. Similarly, semivolatile species might be gases in the hot effluent sampled at a combustion source, but they condense as PM at ambient temperatures.

Some of the most important sources of primary PM are "fugitive" in the sense that their emissions enter the atmosphere as puffs of indeterminate extent released at unpredictable times rather than as well-defined flows through a chimney or tailpipe. Fugitive particle sources, which include wild and prescribed fires, open trash burning, construction activities, agricultural tillage, and unpaved road use, are particularly hard to characterize in terms of activity concentrations and emission factors. All the difficulties are

(Continued)

BOX 3-1 *(Continued)*

heightened when interest extends beyond mass emission rates to include particle composition and size, as needed for health effects studies.

Emission inventories merit scrutiny because they are critical and inherently uncertain inputs to air quality management. A crucial cross-check is provided by comparisons with observed ambient concentrations, receptor models, and inverse applications of source models.

focused on representing PM mass emissions, and it recommended the adaptation of realistic source-test methods and their widespread application to measure mass emissions, chemical composition, and size distributions of PM. The committee also emphasized the characterization of the emission rates of reactive precursor gases (SO_2, oxides of nitrogen [NO_x], ammonia, and volatile and semivolatile organic compounds). The committee's final recommendation was the construction of comprehensive national emissions modeling systems and resulting inventories that are size and chemically resolved. Because particle toxicological studies are ongoing, and air quality simulation models for state implementation plans (SIPs) are currently being developed and tested, the committee called attention to the need for immediately starting research to improve the characterization of PM emission sources.

What Has Been Learned?

Substantial improvements have been made since 1997 in estimates of on-road mobile-source emissions, particularly from heavy-duty diesel trucks and buses, though significant uncertainties remain even for this source category. A national, multisponsor effort, involving EPA, was made to implement standardized test methods (Gautam et al. 2002) and conduct an intercomparison study of mobile-source emissions testing facilities in the United States (Traver 2002). Effects on emissions of changes in fuels (for example, low sulfur diesel and compressed natural gas), after-treatment devices (for example, catalyzed particle trap), and operating conditions have also been characterized; the findings have informed recent regulatory decisions by EPA and California's Air Resources Board (CARB)—among

TABLE 3-1 General Descriptions of Particulate Matter Emissions and Source Types

	Emissions	General Source Types
Primary	Crustal, soil dust, and road dust	Paved and unpaved roads, vehicle tire and brake wear, construction, agricultural and forestry operations, high wind events, and fires
	Salt (NaCl)	Oceans, road salt, and salt pans/dry lake beds
	Biogenic material	Pollen, spores, and plant waxes
	Metals	Industrial processes and transportation
	Black carbon	Fossil fuel combustion (especially diesel engines)
	Semivolatile organic compounds (direct condensation of organic vapors at ambient conditions) and nonvolatile organic compounds	Contemporary and fossil fuel combustion, surface coatings and solvents, and industrial processes, forest fires, and biomass burning
Secondary	Semivolatile and volatile organic compounds (forming secondary organic aerosols)	
	Sulfur dioxide (forming sulfate particles	Electrical utilities, transportation, mining, smelting, and other industrial processes
	Ammonia (contributing to formation of ammonium sulfate and ammonium nitrate)	Agriculture and animal husbandry, with minimal contributions from transportation and industrial processes
	Nitrogen oxides (forming ammonium nitrate with ammonia)	All types of fossil fuel combustion and, to minor degree, microbial processes in soils

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them, the adoption by CARB of emission standards for 2007 and subsequent model-year on-road heavy-duty (diesel) engine designs that are expected to yield a 90% reduction of NO_x emissions, 72% reduction of nonmethane hydrocarbon (NMHC) emissions, and 90% reduction of PM emissions, as compared with previously adopted 2004 model-year emission standards (Lloyd and Cackette 2001). The finding that catalytically controlled gasoline vehicles are a major source of ammonia emissions in urban areas is leading to much improved ammonia emission inventories and research on catalyst formulations to minimize these emissions. Another significant advance has been made in understanding the composition and growth in size of ultrafine particles (less than 0.1 micrometer [μm] in aerodynamic diameter) emitted by heavy-duty diesel trucks and, to a lesser extent, light-duty gasoline vehicles. The data contribute to an understanding of emissions according to vehicle size, engine type, fuel type, and operating conditions. In addition, such data are informing the design of exposure studies (topic 1) and toxicological research (topic 5) on ultrafine particles (for example, in the roadside exposures of animals being carried out in Los Angeles). Little or no information exists, however, to characterize emissions from nonroad engines.

EPA published a national $PM_{2.5}$ emissions inventory using simplistic adjustments to its existing PM_{10} inventory (EPA 2000) but has not yet developed the chemically speciated inventories necessary for understanding relationships between emission sources and airborne PM. EPA has also developed a national emissions inventory for ammonia, but several key sources (for example, natural sources, open burning, humans) are not included (Pace 2002). Such data are needed for developing emission-control strategies for implementation of the $PM_{2.5}$ NAAQS. In addition, the first-ever ultrafine PM emissions inventory was constructed for the Los Angeles air basin (Cass et al. 2000). An EPA-sponsored research program has also quantified the uncertainty in emission inventories for several source types (Frey and Bammi 2002; Frey and Zheng 2002). However, there is still a need for improving the characterization of emission-inventory uncertainties.

What Remains To Be Done?

Although the committee could identify some specific advances in relation to characterization of emission sources, a comprehensive, cohesive emission-characterization research program, as recommended by the committee in its second report (NRC 1999), has not yet been implemented by

EPA and other research sponsors, including the states. A greater leadership role by EPA is needed in relation to this research topic, as some of the needed emissions characterizations will be carried out by the states, industry, and other stakeholders. So far, EPA has assumed this responsibility in a few important areas. EPA-led programs are updating speciation profiles for receptor-oriented models, assessing particle emissions from on-road light-duty gasoline vehicles, and assessing the state of the science and needed research for emission inventories. However, additional test methods that are comparable and representative of the atmosphere need to be developed for sources other than on-road motor vehicles that contribute major fractions of ambient PM (for example, residential wood combustion, wildfires, cooking, and nonroad engines). These methods should be defined in terms of performance rather than design specification to encourage application and innovation to enhance the value of these tests for multiple purposes, including research and regulatory decisionmaking.

PM_{10} emission-source testing methods overestimate mass emissions from stationary sources by adding mass condensed in impingers to the mass collected on a hot in-stack filter. The impinger mass is dominated by dissolved gases instead of captured particles, while the hot filter allows condensable material to pass through it. A new standard method for $PM_{2.5}$ emissions testing method is needed that dilutes samples to ambient temperature conditions and allows for the addition of multiple filters and particle sizing instruments. This method will supply more realistic estimates of primary-particle emission rates, as well as options for obtaining source size distributions and chemical profiles.

Continuous emission monitors (CEMs) on major stationary sources provide the best emission estimates for SO_2 and sometimes for NO_x, but better interfaces are needed to facilitate effective use of this information. Studies are also needed of the comparability of CEM and earlier fuel-based estimates to establish the reality of reported SO_2 emissions declines during the mid-1990s transition period. CEMs for primary-particle emissions should be added when possible.

Methods also need to be developed and applied to better quantify PM and precursor emission rates from in-use engines operating in on-road and nonroad environments. Emission factors based on the CO_2 concentration in exhaust streams can be measured by on-board, in-plume, or remote-sensing analyzers for NO_x, CO, and hydrocarbons. Analogous systems to measure particle mass emissions and size distributions have been demonstrated, but they need to be further developed, tested, and applied. Deviations between engine compliance tests of a few vehicles on dynamometers

and real-world engines, fuels, and operating conditions need to be characterized and their basis understood. High-emitting vehicles and cold starts, off-cycle, and nonroad engine emissions may have PM characteristics that differ substantially from those of federal test certification tests.

Emissions from nonanthropogenic sources are poorly estimated. These are typically fugitive and intermittent with particle characteristics that temporally vary and are accordingly difficult to characterize directly. In many situations, their contributions to ambient loadings may be more reliably determined from detailed ambient measurements and simple source-receptor modeling of the tracer/mass-balance variety. As the committee has recommended previously, the three activities—emissions tracking, air quality modeling, and ambient monitoring—need to be viewed as complementary and yielding reinforcing evidence.

Static emission inventories, typical of those used for tracking annual trends, are insufficient for estimating the variability in aerosol properties using air quality models. In addition, emissions from other than anthropogenic sources are poorly estimated.

Common geographic information system (GIS) land-use maps for soil types, land use, vegetation, and roadways need to be assembled for easy access and common usage. Because many emissions are meteorologically dependent, time-specific estimates of temperature, relative humidity, and wind need to be developed for input to emission-generation models. The same meteorological fields used to drive air quality models can be employed, if needed, to support emission simulations. Another approach is to use temperature fields developed more directly from observations. Source profiles of PM and volatile organic compounds need to be identified, evaluated, documented, and compiled into databases that can be used to provide emission rates for specific substances and for receptor model source apportionment. In general, the committee concurs with the conclusion of NARSTO (2003) that both direct and precusor sources of carbon emissions are the most poorly characterized of the emissions contributing to PM.

As the committee emphasized in its third report (NRC 2001), EPA should develop a comprehensive plan for systematically applying new source-test methods to develop a complete, comprehensive national emissions inventory based on contemporary source tests of comparable quality. The timeline for this testing must allow for the incorporation of revised and updated data into an overall emissions inventory of predetermined quality and completeness by the time the next round of state implementation plans for PM must be drafted. The emission factors developed from source testing should also be used to more frequently update AP-42 (EPA 1995), which

is a widely used compilation of emission factors. There is also a need for more efforts to estimate the uncertainties in emission inventories.

RESEARCH TOPIC 4. AIR QUALITY MODEL DEVELOPMENT AND TESTING

What are the linkages between emission sources and ambient concentrations of the biologically important components of particulate matter?

Introduction

Regulators' actions to limit pollutant exposures have direct effects on emissions from sources rather than on concentrations in ambient air. An understanding of the relationship between emissions and atmospheric concentrations is thus a key input to regulatory decisionmaking. To understand the effects on human health, such concentration changes need to be linked to changes in human exposure.

Source emissions can be linked to ambient concentrations either prognostically, through mechanistic modeling and numerical simulation, or diagnostically, through inferential analysis and mathematical inversion. The prognostic approach, known as source-oriented or chemical-transport modeling, uses measured or estimated emission rates, chemical-reaction schemes, meteorological data, and numerical algorithms to simulate the concentrations expected to result in the ambient air for a given set of emissions. Regulators have historically tended to favor this approach because it takes emissions, the physical parameter most directly affected by their policy decisions, as an explicit model input variable whose effects on air quality can be directly explored under any desired scenario. The diagnostic approach, known as receptor-oriented analysis or receptor modeling, begins instead with ambient samples of pollutants and uses various forensic techniques to trace them back to their sources. Although the source-oriented approach is naturally suited to "what-if" analyses, receptor-oriented tools can offer relatively more direct and persuasive evidence of what is.

To be operationally useful, models must be able to interface with routinely available data on emissions and ambient concentrations. NRC (1999) stressed the need to view the three activities of emissions tracking, source-receptor modeling, and ambient monitoring as integrated processes that continually cross-check and feed back on one another, each component supporting the others. Source-receptor modeling and the evaluation of

prognostic models rests essentially on EPA's "nonresearch" monitoring activities in much the same way that epidemiology rests on an infrastructure of routine public health reporting and environmental monitoring. Thus, the committee, in its second and third reports, recognized a significant need for funding technical activities necessary to support emissions characterization and model development.

What Has Been Accomplished?

Atmospheric Processes

EPA is continuing to carry out research on the processes on which models are based. There has been some support of the following specific atmospheric processes:

- Nucleation
- Uptake of water and thermodynamic properties of aerosols, especially organics
- Secondary organic aerosol formation
- Representation of aqueous chemistry
- Dry deposition
- Sub-grid scale processes and vertical mixing
- Inclusion of the effects of particles on radiation
- Methods to determine the effect of large-scale meteorological processes on long-term particle concentration

Data Infrastructure

EPA established a speciation trends network (STN) of 54 sites to quantify ambient $PM_{2.5}$ chemical composition in urban areas and encouraged and supported local and state agencies to enhance these with additional sites. EPA also increased continuous hourly $PM_{2.5}$ monitoring from 50 sites in 1997 to about 200 sites in 2002. It supported the near-doubling of the number of monitors to 160 sites in the IMPROVE network at national parks and wilderness areas to provide nonurban $PM_{2.5}$ mass and composition. Eight EPA PM "Supersites" were established, emphasizing method testing and evaluation and continuous monitoring of precursor gases, mass, sulfate, nitrate, carbon, and size distributions with a variety of established and

emerging technologies. The Supersite in Atlanta operated for one month, August 1999, to evaluate new and emerging technologies for characterizing ambient PM.

An improved understanding of the composition and variability of airborne PM is expected to be obtained from increased monitoring efforts. For example, the composition of $PM_{2.5}$ mass at representative urban and rural locations in North America is shown in Figure 3-1. Sulfate-containing particles make up a major fraction of airborne $PM_{2.5}$ in the eastern United States. In parts of the western United States, nitrate-containing particles are a substantial component. Carbonaceous material contributes a substantial fraction in all the measured locations. Measured data for black carbon and organic carbon are relatively imprecise because the results are method-dependent although their total is fairly consistent among methods (Chow et al 2001).

Source-Oriented Models

In 1998, when the committee's first report was released, the scientific community had air quality models incorporating the atmospheric processing of particles. However, little systematic testing had been carried out against appropriate field data, and a number of important processes were not mechanistically represented. A limited number of research projects were funded from 1997 to mid-2001 related to improving the representation of processes in atmospheric particulate models.

Surveys have since appeared that critically review the models' strengths, limitations, and uncertainties as applied to air quality management (Seigneur, 2003; NARSTO, 2003). Most model applications are limited with respect to evaluation due to lack of (1) standardized evaluation methods and software to implement them, (2) appropriate ambient and source measurements, (3) human resources, and (4) transparency and detailed documentation for model evaluation. An additional critical need is to develop and evaluate approaches for estimation of annual averages, as the most sophisticated models are designed to run limited duration simulations of specific episodic periods. Seigneur et al. (2000) recommended that models not be used until completion of an exhaustive performance evaluation including the following: (1) operational testing that demonstrates an ability to estimate PM and its chemical components; (2) diagnostic testing that examines the degree to which precursor and intermediate concentrations are reproduced; (3) mechanistic testing that determines the effects of

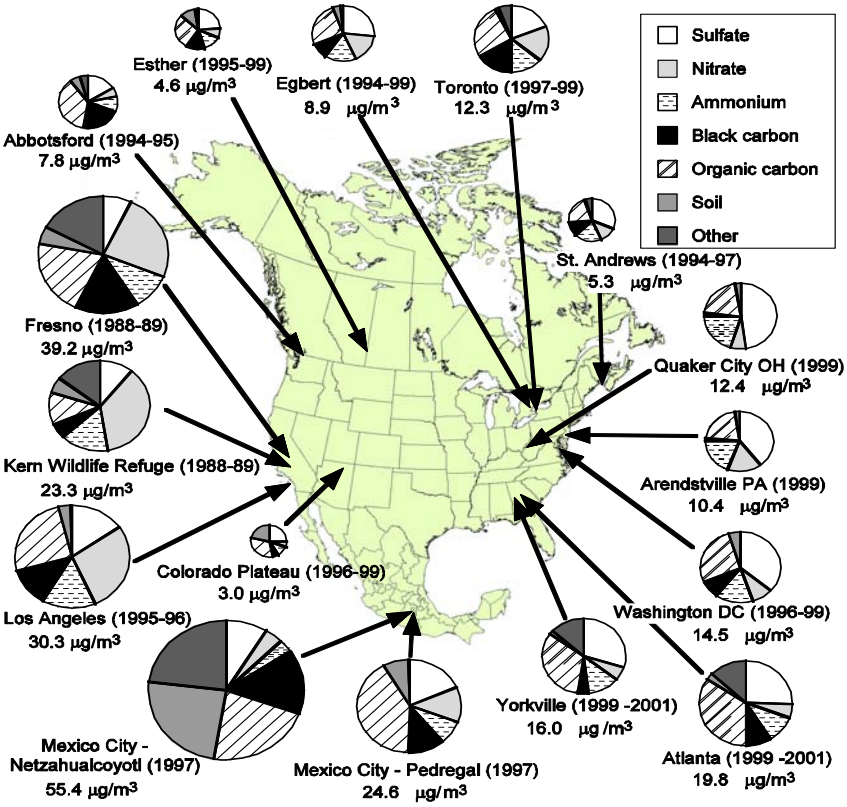

FIGURE 3-1 Composition of $PM_{2.5}$ at representative urban and rural locations. The urban sites are Toronto; Washington, DC; Atlanta; Mexico City; Los Angeles; and Fresno. Averaging periods and average $PM_{2.5}$ mass are indicated. All sites have at least 1 year of sampling except Mexico City, for which the average was determined for 14 days in 1 month. More recent short-term measurements from December 1995 and January 1996 at Fresno and Kern Wildlife refuge show lower $PM_{2.5}$ mass concentrations but similar composition to the data displayed here. The Colorado Plateau data are the averages of the IMPROVE sites located at Bryce Canyon, Canyonlands, Grand Canyon, Petrified Forest, Mesa Verde, and Zion National Parks. Source: NARSTO 2003. Reprinted with permission; copyright 2003, EPRI, Palo Alto, CA.

emission and meteorological changes on estimated concentrations; and (4) probabilistic testing that quantifies uncertainties in model results. Roth (1999) specified issues that should be addressed in writing prior to the application of a model by the end user community. However, the commit-

tee recognizes that, in most cases, the time and cost required for rigorous validation of an air quality model application exceeds available resources.

From 1998 to 2002, EPA released both the new modeling framework, Models-3, and upgraded versions of the Community Multiscale Air Quality (CMAQ) Program, the chemical-transport modeling component intended for modeling gas-phase and particulate pollutants. The work on Models-3/CMAQ has been done intramurally at EPA with some interaction with other model developers. Concerns about difficulty in setting up Models-3 provided impetus for developing the new Java-language-based graphical framework now used for its implementation, the multimedia integrated modeling system (MIMS). Although publicity of Models-3 as a potentially widely used tool has been substantial, considerable additional review and effort are needed to make it easily transferable to an end-user community. However, significantly more use of Models-3/CMAQ is underway by various research groups as well as regional planning organizations (RPOs).

Models-3 was run on a few air pollution episodes from the early 1990s within the eastern United States, and the results were compared with ambient monitoring data without accounting for sampling artifacts (see Kirchstetter et al. 2001) and analytical distinctions (Chow et al. 2001) that are known to affect the data. In addition, the lack of sufficiently accurate emission inventories (whose improvement is related to Research Topic 3) hampers the implementation and evaluation of any air quality model. As of March, 2002, it used a thermodynamic equilibrium model to calculate the concentrations of volatile species, an assumption that may not be valid. Much more effort is needed to test the model and to ensure its accurate operation over the entire spatial domain of the United States. The committee had suggested the need for a series of major field studies that would provide suitable test data. There was an effort to coordinate monitoring done across the eastern United States during two months in 2001 and 2002 as part of the Supersites Program, but these data cover a limited temporal and spatial domain. Substantial additional monitoring data will be needed for model evaluation to provide adequate confidence in Models-3's ability to adequately predict the PM and PM component concentrations. The Western Regional Air Partnership (WRAP) is testing and applying CMAQ in the west. The California Air Resources Board plans to use CMAQ to model air pollution episodes. There are some data sets available for model evaluations that represent different combinations of emissions, meteorology, and transformation properties than those encountered in the eastern United States, but these are not being fully exploited for model evaluation. Some of these field studies are briefly described in the discussion on special monitoring studies in Appendix C.

Efforts inside and outside EPA are under way to link and integrate air quality models with exposure and dose models (Burke et al. 2001; Glen 2002; Rosenbaum 2002). The committee recognizes that source-oriented air quality models are primarily used to determine how area-wide emission reductions will affect the ambient concentrations used for compliance purposes. However, the issues of health exposure lie clearly in the finest grid to subgrid scale of urban modeling (less than 4 km). The committee recognized the need to improve the bridge between the scales typically used for PM source-oriented modeling and those needed to conduct exposure assessment. Examples of such approaches are described in the references above as well as in Georgopoulos et al (in press). In addition, while large spatial scales may be acceptable for estimating certain PM components, simulation of ambient concentrations for other primary emissions and for ultrafine particles will require sub-4-km grid scale estimations. Further work is needed to improve the simulation of processes on such scales to match with exposure models and to provide appropriate data for the testing of models across scales.

Chemical-specific modeling and normalization to measured chemical concentrations are major advances in using models to demonstrate an area's plans for attaining the PM NAAQS. These improvements enable a shift away from modeling $PM_{2.5}$ or PM_{10} mass regardless of its composition, as has been the case in the past when SO_2 emissions and fugitive dust would both be assessed on a similar basis regarding their contributions to total mass. Reductions in SO_2 emissions can now be assessed on the basis of changes in sulfate mass rather than the entire PM mass. Evaluations of CMAQ indicate that the model performs best in representing sulfate mass, and less well in representing nitrate and overall $PM_{2.5}$ mass. A key to improving the performance of CMAQ and other source-oriented air quality models is enhancing their treatment of the carbonaceous component. NARSTO (2003) contains a detailed summary of the strengths and weakness of current source-oriented air quality models.

Receptor-Oriented Models

There has been some progress in receptor-oriented analysis since 1997, albeit much remains to be done. A refinement of conventional factor analysis has been developed, known as positive matrix factorization (PMF), that allows for analyses to include data for species that are undetectable in some samples (Paatero and Tapper 1994; Paatero 1997; Hopke 2000). EPA has supported the development and testing of UNMIX, another multi-

variate approach to extracting the compositions of sources' emissions from observed correlations between chemical species' concentrations in multiple samples (Henry 2000; Henry and Norris 2002). Chemical mass balance (CMB) modeling (Watson et al. 1998a), which uses knowledge of speciated emissions to apportion source contributions in individual samples, is increasingly incorporating speciated organic measurements or operationally defined organic fractions (Jeon et al. 2001) to distinguish source categories with similar elemental compositions (Watson et al. 1998b; White and Gunst 2001; Schauer et al. 2002).

Several collaborations between proponents of different receptor-oriented tools have taken place since 1997, significantly clarifying the capabilities and limitations of the overall approach (Pitchford et al. 1999; Poirot et al. 2001; Willis 2001). In various combinations, the speciation-based methods CMB, UNMIX, and PMF have been compared with each other and with other methods that are based on spatial correlation and estimated air-mass trajectories. A conclusion that emerges from these exercises is that analysts using different methods benefit from interacting with each other and comparing results. Any single approach leaves some ambiguities unresolved, and a second approach, with its own but different limitations, can provide additional insights. Moreover, investigators regularly discovered previously overlooked data issues while searching for the causes of disagreements, highlighting the need for characterization of data quality as an important issue for the new monitoring networks.

What Remains To Be Done?

EPA's ultimate goal should be to have integrated, flexible, and well-tested particle models available on a timely basis for distribution and use in PM management strategy development. These models need to be evaluated with ambient measurements along with emission rates, source profiles, and meteorological measurements. It is still not clear that EPA is making the appropriate commitment needed to have the best models available for ready use at the local air quality management levels. Coupled with little progress on emissions characterization for emission rates and source profiles, the committee has substantial concerns about the air quality management community's access to fully operational tools and databases needed for NAAQS implementation.

Although the instruments needed to monitor air quality are largely in place, much remains to be done if the data they produce are to be used effectively for both research and NAAQS implementation. At the most

basic level, the data must first be made less difficult for researchers and other potential users outside EPA to access. The web portal that once served this function has since 2001 been replaced by AirData 2003. "Hourly and daily air monitoring values (raw data) are not available. To obtain hourly or daily monitoring values, submit a Freedom of Information Act request to EPA." There are substantial sampling and analytical uncertainties to be addressed in the measurement of major particle species, most critically organic material. More generally, EPA needs to articulate a plan for continuing comparisons that systematically test its emissions data, source and receptor models, and ambient data against each other.

EPA must now provide the leadership for a coordinated effort to compare various models and their implementations with one another and to incorporate refinements developed in academic and other research institutions to improve those models earmarked for regulatory applications. This task will require greater attention to characterizing emissions and the development of the large-scale, three-dimensional field studies that are necessary for rigorous evaluation of source-oriented models. Although EPA may not have substantial resources for model evaluation, it can participate in and help to shape efforts involving other government agencies and private institutions with substantial field programs, synergistically enhancing the value of the resulting data for its own applications. Moreover, coordination among the research activities directed at topics 3 and 4 could help speed progress in development of accurate methods for control of toxic particles. For example, a systematic effort to examine whether the results of air quality models are consistent with the emissions and models in a variety of different regions would aid in improving sources and in expending funds for source inventory work in the most critical areas. Examining whether the extent to which models and emissions can inform epidemiological studies could speed progress on understanding the toxicity determining characteristics of particles.

U.S. EPA (2001) recognizes that air quality models have inherent uncertainties due to limitations in scientific understanding of source-receptor relationships as well as insufficient model input data. A weight of evidence approach is described that includes a core set of analyses consisting of (1) several (not a single) air quality models, (2) descriptive analysis of observed air quality and estimated emission trends, and (3) observational models. Limited science and measurements "make the ability of a model to accurately predict concentrations of $PM_{2.5}$ and its components at a given time and location doubtful." Rather than provide absolute end products (such as $PM_{2.5}$ mass or light extinction) for comparison with a standard,

relative contributions to each of the $PM_{2.5}$ components—sulfate (SO_4^{2-}), nitrate (NO_3^-), organic carbon (OC), elementary carbon (EC), primary inorganic material, and unidentified mass (difference between measured mass and components)—are modeled. Emission reductions are chemical-specific (that is, SO_2 reductions for SO_4^{2-}, vehicle exhaust and vegetative burning reductions for carbon), and their effects are normalized to the total amount of each material in ambient samples.

Steps in EPA's guidance are to: (1) form a conceptual model of the emissions, meteorology, and chemical transformations that are likely to affect haze; (2) develop a modeling/data analysis protocol with stakeholders that is consistent with available science, measurements, and the conceptual model; (3) construct and evaluate an emissions inventory for the domain that might affect haze as indicated by the conceptual model; (4) assemble and evaluate meteorological measurements for the domain; (5) apply the specified air quality models and data analyses and compare with ambient concentrations; (6) apply diagnostic tests and justify discarding results that are not physically reasonable; (7) modify the inventory to reflect different emission reduction strategies in consultation with stakeholders, and evaluate the effects of reductions at receptors; (8) make models, input data, and results available to others for external review; and (9) judge the weight of evidence supporting or opposing the selected emission reduction strategy prior to implementation. These ideas are further developed by NARSTO (2003), which made numerous specific recommendations that EPA and other sponsoring agencies should seriously consider when planning further modeling efforts.

Simpler, more user-friendly software is also needed to explore and understand such concepts as (1) which subregions contribute most often and contain the highest emissions; (2) how fast or slow precursor pollutants turn into particles when injected into polluted and unpolluted environments; (3) where and when different precursors limit or enhance particle formation; (4) how pollutants might be removed in the gas phase much faster than in the particle phase; and (5) what the multiple effects of NO_x and VOC emissions are on O_3, SO_4^{2-}, NO_3^-), and secondary organic aerosol. Such information would help decisionmakers decide what is knowable and what can be better known with a modest investment.

This nation is proceeding to implement the NAAQS without properly evaluated models to confirm their accuracy. There is a critical need to develop field programs that can provide a full set of validation data so that air quality particulate models can be tested for their ability to estimate ambient concentrations. These programs should proceed in a variety of air

quality settings so that the capability of the model to represent particles across a range of pollutant and natural concentrations can be evaluated. These field programs should include the development of an accurate inventory of particles and their precursors in the regions selected for study. The assumptions currently made in Models-3/CMAQS should also be examined to develop a proper understanding of whether these assumptions affect control strategies. Models-3/CMAQ should be documented and made easily available to the academic community so that its expertise can be deployed by helping to make model improvements and so that the model can be made available to the end-user community, who will need to devise control strategies. EPA has taken a step in this direction with its Community Modeling and Analysis System, which is intended to facilitate development and application by the user comments.

The adequacy of air quality models used to target specific types of emission sources will have to be evaluated within the evolving context of determining which features of particle exposures are most relevant to health risks. At the same time, the interpretation of health-effects findings will have to reflect an understanding of source-ambient relationships in the atmosphere. Therefore, health-effects and atmospheric scientists must enhance interdisciplinary collaboration through a continuous exchange of information.

RESEARCH TOPIC 5. ASSESS HAZARDOUS PARTICULATE MATTER COMPONENTS

What is the role of physicochemical characteristics of particulate matter in eliciting adverse health effects?

Introduction

Particulate matter in ambient air is a mixture of different types of particles, having different sizes and chemical composition, and originating from many different sources, both primary and secondary. In urban air, particle numbers and mass concentrations vary across the size spectrum from the tiniest particles sized in nanometers, equivalent to molecular clusters, to very large particles, such as pollen grains and windblown sand. With current measurement methods, a rich set of elements and chemical compounds can be identified in particles, revealing wide variations in composition even among particles of the same size.

In spite of the complexity of airborne particles, mass-based standards for particle concentrations in air (for example, the $PM_{2.5}$ NAAQS) implicitly assume the same risk to health from all particles, regardless of specific physicochemical characteristics. Mass-based standards have been maintained, even though there has long been evidence from laboratory experiments that specific characteristics may be relevant to determining health effects. However, the evidence has not led to alternative standards that also incorporate composition. A better understanding of these characteristics of particles that modulate toxicity could result in targeted control strategies that would specifically address these sources having the most significant effects on public health. Some of the physicochemical characteristics that may influence toxicity are presented in Table 3-2. However, it is unlikely that any single characteristic is predictive of risk for all health effects associated with exposure to ambient PM.

What Has Been Learned?

Despite the large number of research projects directed at topic 5, research progress has been limited over the last 5 years, reflecting the challenging question that is being asked. The diversity of PM characteristics and the array of possible health effects, as well as the potential for different features of particles to be relevant to different health outcomes, define a potentially large matrix for investigation. Thus, research directed at topic 5 should provide insight into how particle characteristics determine toxicity and into the health impacts associated with the different characteristics. Research on this topic has appropriately involved both epidemiological and toxicological approaches.

Epidemiological studies have been substantially hampered by the lack of air quality monitoring data that characterize particles using parameters other than mass. Large-scale studies will need to build from a monitoring platform that can be used to estimate exposures for study participants and communities. Monitoring for PM_{10} continues, and the network for $PM_{2.5}$ is now in place and the methods are being developed for monitoring $PM_{10\text{-}2.5}$. The Supersites Program has provided insights into the complexity of PM covered by this initiative, and the Speciation Trends Network should provide a platform for epidemiological studies directed at assessing particle characteristics and public health. However, these programs still fall far short of encompassing the full range of particle characteristics that may influence health. For example, measurements of ultrafine particles have been made at only a few locations, measurements of organic compounds are

TABLE 3-2 Examples of Particulate Matter Characteristics Potentially Important to Health Responses

Physical Characteristics	
Size	Coarse, fine, ultrafine
Surface	Surface and mass ratio, physical vs. functional surface, biological absorption characteristics
Morphology	Spherical, aggregate, fibrous
Mass concentration	Total mass, size-specific mass, airborne PM mass vs. filter-derived mass
Number concentration	
Charge	
Physical Chemistry	
Hygroscopicity, lipophilicity, hydrophilicity	
Bioavailability	Solubility in biological media, penetrance, and distribution
Acidity	
Oxidant potential	
Surface vs. core chemistry	Surface reactions, adsorbed materials
Chemical Components	
Metals	Transition vs. other valence state
Carbon	Elemental, temperature-resolved fractions, organic (by class and species), semivolatile (particle and vapor partitioning), adsorbed volatile organic compounds
Biogenic	Antigens, microorganisms, toxins (endotoxin and other), plant and animal debris
Secondary inorganic aerosols	Sulfates, nitrates
Dusts	Crustal minerals (crystalline state), street dust (tire brake and road wear)
PM as a component of air pollution	Interactions with other pollutants (other than additive) and with other environmental variables (such as weather)

sparse, and metals are measured as total metallic species rather than as soluble metals, which are thought to be more biologically relevant.

Although specific research projects have measured some of the components of PM in ambient air, few have made a comprehensive set of measurements. Several studies have examined both the fine ($PM_{2.5}$) and coarse ($PM_{10-2.5}$, particles between 2.5 and 10 μm) fraction of PM_{10}; these studies indicate that both fractions can be associated with health responses, although the relevant outcome indicators may not be the same for both fractions. Epidemiological studies have considered the ultrafine fraction of PM; the results are decidedly mixed, with positive and negative associations with health measures (for example, Peters et al. 1997; Tolbert et al. 2000a; Osunsanya et al. 2001). Of the studies that have examined specific chemical fractions of PM, differences have been found in the toxicities associated with the different fractions; however, only a few studies provide relevant data, and overall inferences cannot as yet be made about those chemical fractions of PM that may be of greater or lesser health concern.

The body of evidence from toxicological studies is more substantial. However, interpretation of the results from many of the studies is constrained by the high exposure or dose concentrations that have been used, often well beyond the range of human exposures to ambient air pollution. Although some evidence for toxicity has been found in relation to virtually all the fractions of PM examined, the relevance of these findings to human responses at ambient concentrations is uncertain, given the high exposure concentrations used.

Toxicological research on PM components has not been coordinated to systematically address the array of components and associated health outcomes. Instead, investigators have examined the toxicity of different sets of components using different protocols and toxicological outcomes. As a consequence, comparisons across studies to assess relative toxicity of PM from different sources and of different components cannot be readily made. Nevertheless, evidence from toxicological studies directed at PM has provided some insights about various PM fractions that may be associated with adverse health outcomes, and the extent of this evidence has increased over the past 5 years.

Research has indicated that particle surface area, especially for ultrafine particles, may play a role in some adverse effects, such as pulmonary inflammation. Some responses are related more strongly to that metric than particle mass for this size mode (Oberdörster 1996). Data also indicate that greater pulmonary response appears to be consistently produced by ultrafine particles than by fine particles that have the same chemical composition (Oberdörster et al. 1992; Li et al. 1999). On the other hand, some studies

suggest that specific chemical composition rather than particle size predicts biological response (Wellenius et al. 2003). Thus, the relative roles of size and composition in determining toxicity of ambient PM have not been definitively clarified.

Over the past 5 years, certain chemical components of PM have received more research attention than others, not necessarily in proportion to the relative abundance of these components in ambient PM. For example, considerable emphasis has been given to the role of transition metals in determining responses in toxicological models. Several studies have found that metals, especially the water-soluble fractions, are associated with health-response indicators (Frampton et al. 1999; Campen et al 2002). These components have been associated with various effects, including production of reactive oxygen species, pulmonary inflammation, enhanced sensitization to antigens, and increased susceptibility to respiratory tract infection. There is also some indication that these species play a role in cardiac effects as well.

Organic components of PM have received little emphasis. For example, although bioaerosols can affect toxicity, study results are too limited to reach any overall conclusions. Among the many organic components of PM, those associated with diesel particles have received the most attention. Results to date suggest that greater emphasis on PM-borne organics from many sources is warranted.

Although research related to topic 5 has not provided substantial new evidence for directing regulatory policies and source control, the accumulating literature has begun to steer researchers toward the more promising PM characteristics. For example, there has been a shift in emphasis to metals particularly those that are water soluble; such emphasis had previously been placed on sulfates as a major toxicity-determining component of ambient PM. However, current knowledge from toxicological studies suggests that the health impacts of sulfates per se are less than proportional to their contribution to ambient PM mass (Heyder et al. 1999; Schlesinger and Cassee 2003). Despite these advances, research attention has not been given to the full range of particle characteristics that may be important, and it is not evident that a coordinated strategy is in place to ensure that the most promising hypotheses are targeted and given priority and that screening approaches are continued across the array of PM characteristics.

What Remains To Be Done?

Since the committee's first report in 1998, an increasing number of

studies have examined a widening range of particulate chemical and size characteristics. The results of these studies have not been consistent; thus, the array of particle characteristics that modulate the toxicity of ambient PM cannot be greatly narrowed down to bring greater focus to research on topic 5. Neither have these efforts provided much insight into how specific PM characteristics play into interactions between PM and other pollutants.

Few conclusions regarding the health significance of particle characteristics have resulted from epidemiological research, because monitoring data in most locations have not been sufficient to support epidemiological research relevant to topic 5. The small number of published epidemiological studies that have examined particle characteristics in addition to mass do not lead to any certain conclusions on the characteristics that are predictive of risk to populations. Some characteristics, such as carbon content, warrant further investigation (for example, Tolbert et al. 2000b, Metzger et al. 2004). Toxicological and epidemiological studies also need to be better integrated to ensure complementary findings, thus building a solid platform of evidence on particle characteristics. Parallel evidence from these two areas of investigation, along with greater understanding of mechanisms, will reduce uncertainty in making extrapolations from high-exposure subjects to those experienced more widely by the general population.

The committee's review concludes that, despite the increased research effort, the uncertainties related to topic 5 generally remain comparable to those described in the committee's first report, although some evidence indicates that toxicity may be related to specific characteristics, such as metals. The studies conducted over the past 5 years indicate the difficulty of the scientific questions and the need for new research approaches, whether toxicological or epidemiological. Although some progress has been made, suggesting links of some physical and chemical characteristics of particles to toxicity, research on topic 5 remains incomplete.

A strategy is needed to ensure that toxicological and epidemiological research is directed toward a greater range of particle characteristics than studied to date, including bio-derived components of PM. Such a strategy might incorporate both the application of uniform protocols to multiple characteristics and the use of a wider range of investigator-initiated approaches. The goal would be to ensure that no potentially important characteristic is overlooked and that the totality of potential health outcomes is considered for each characteristic. Differences in the spatial homogeneity and measurement error associated with different components of PM need to be addressed in the design and analysis of epidemiological studies to ensure that all components are appropriately considered. Finally, the health significance of specific particle characteristics must be considered in rela-

tion to their modulating effects on interactions with other particles or nonparticulate pollutants.

To date, toxicological studies of PM characteristics have been largely designed to determine whether a single physical (such as PM size) or chemical (such as soluble transition metal) characteristic could be linked to adverse health responses. Future work needs to extend these investigations in four key dimensions: (1) addressing those characteristics that have received little attention; (2) defining exposure-dose-response relationships at realistic exposures; (3) making direct comparisons between PM with different characteristics using identical protocols; and (4) evaluating the importance and role of the characteristic in question as it exists as a component of realistically complex exposures.

Work to date predicated on the hypotheses of individual investigators has addressed several but certainly not all of the physicochemical characteristics outlined in Table 3-2. For example, work on ultrafine PM has focused almost entirely on solid particles, despite the fact that much of the ultrafine PM mass consists of nonsolid condensed organic matter (Sakurai et al. 2003). Similarly, a substantial effort has been directed toward the oxidative-driven inflammatory and cytotoxic responses to water-soluble transition metals (Donaldson et al. 1997; Ghio et al. 2000a), but very little emphasis has been placed on the inflammatory and cytotoxic effects of PM-bound organic compounds, despite the evidence that this fraction can also operate through oxidative reactions (Li et al. 2002; Yu et al 2002; Reed et al. 2003).

Only a few attempts have been made to directly compare responses and dose-response relationships for different types of particles. Although it is understandable that different protocols would be used to explore effects and mechanisms for different PM characteristics and initial explorations may begin at high doses, an understanding of the relative importance of these characteristics also requires using the same experimental protocol related to a particular health outcome directly compare the exposure-dose-response relationships (that is, relative toxicity and no-effects levels) of different types of particles. Finally, to complete understanding of the risks of PM, as modified by its characteristics, studies will be needed that further characterize the toxicity of PM as it exists within the urban atmosphere, along with many other injurious pollutants. The increase in toxicity of diesel soot after exposure to ozone (Madden et al. 2000), for example, suggests the importance of interactions between particles and other pollutants.

Investigation of multiple PM characteristics will present a challenge for epidemiological studies. Many of the measures of particle components and characteristics are highly correlated, making it difficult to separately

characterize the risks associated with some particular characteristics. Using multivariate approaches, clustering of characteristics can be identified and measures of exposure developed for particular PM groups, as defined by multiple characteristics. It may also be possible to address the risks associated with particles that can be traced back to particular source groups, such as mobile sources. Epidemiological studies related to topic 5 will probably need larger numbers of observations, given the multiplicity of characteristics of interest, their clustering, and the relatively weak associations that have been observed with PM mass indexes. Cross-sectional studies may not be adequate for this topic, as variation in exposure is defined geographically, implying the need for many locations. Once the proper monitoring systems are established, time-series studies may be informative for topic 5, but substantial data sets will probably be needed to have sufficient spatial and temporal heterogeneity of exposures to test hypotheses related to PM characteristics.

An alternative to the consideration of components themselves is the consideration of source categories or source indices. For example, studies have been undertaken in which risks to health of individuals living near busy roadways have been addressed by comparison with persons living farther from the roadways. These studies have addressed one particular source, vehicular traffic, but assessments of the pollutants contributing to the increased risk associated with traffic exposure have not yet been made. There will be a need to address tailpipe emissions of gases and particles, as well as particles tied to the mechanical force of road traffic and particles generated by brake use and tire wear.

Another approach is to use a multivariable method—principal components or factor analysis of the various PM characteristics—in an effort to reduce the PM characteristics to clustered and uncorrelated sets (see topic 10). The difficulties with this approach are that (1) the resulting set of variables might not be readily interpreted; and (2) it might not be consistent over time and for different locations. The task remains to identify the most predictive characteristics within the cluster.

RESEARCH TOPIC 6. DOSIMETRY: DEPOSITION AND FATE OF PARTICLES IN THE RESPIRATORY TRACT

What are the deposition patterns and fate of particles in the respiratory tract of individuals belonging to presumed susceptible subpopulations?

Introduction

Dosimetry provides a critical link between particle exposures and the doses of particles reaching critical sites in the respiratory tract, the clearance of particles from those sites, and the movement of particles from the respiratory tract to other organs. Particle dosimetry is largely accomplished using mathematical models of the lung that are based on understanding of its anatomic structure and physiological functioning. Although relatively refined models have been developed over the past 40 years, largely for the purpose of radiation protection, limited emphasis has been given to particle dosimetry in the susceptible subpopulations of greatest concern with regard to airborne particles, particularly persons with underlying heart or lung disease. It is important to understand that the site of concern for deposition or translocation varies among the different health effects, such as nasal deposition for allergic rhinitis, airway deposition for asthma, or alveolar deposition for reduced resistance to pneumonia.

What Has Been Learned?

The greatest policy-relevant advance in the understanding of PM dosimetry since the committee's first report has been the convergence of evidence from multiple studies in multiple laboratories demonstrating an increase in the portion of inhaled $PM_{2.5}$ depositing in the respiratory tract of people having common respiratory abnormalities compared with people having normal lungs. It now appears that as a general principle, any abnormality of airway structure or intrapulmonary gas distribution is likely to increase the total deposited dose for a given exposure concentration (Kim and Kang 1997; Kohlhäufl et al. 1999). The increase in deposition can be substantial; for example, 2-fold increases have been measured in people with COPD (Bennett et al. 1997; Kim and Kang 1997). In addition, increasingly sophisticated deposition models indicate that abnormalities of respiratory structure and airway function also tend to decrease the homogeneity of PM deposition and increase deposition at localized "hot spots" within the lung, which might even further increase doses in localized areas. This growing body of evidence suggests that the increased susceptibility of subpopulations having respiratory abnormalities could be due to a greater dose of PM, to a greater responsiveness per dose unit, or to a combination of those two factors. This knowledge has implications for evaluating the mechanisms of susceptibility and for understanding the relationships among

exposure, dose, and response. It is still uncertain whether deposition might be altered with aging in normal individuals. Unfortunately, there also remains a dearth of information on deposition or clearance in animal models of human diseases associated with increased susceptibility.

Knowledge of the impacts of other host factors on PM deposition has also advanced. There is a better understanding of differences in total and regional deposition between men and women and between adults and children and with variations in breathing pattern (Jaques and Kim 2000). For example, children appear to receive higher doses per unit of respiratory tract surface than adults (Musante and Martonen 2000). There has been less work on clearance; indeed, knowledge of PM clearance in subjects with respiratory tract abnormalities has not advanced substantially in recent years.

There have been substantial refinements of mathematical models for estimating PM deposition, taking into account an expanded range of variables having to do with differences in age and gender, variations in the physical structure of the airways, ventilation rate, respiratory pattern, and PM characteristics (Musante and Martonen 2000; Segal et al. 2000, 2002). These refinements purport to improve the accuracy of estimates of total and regional dose in different subpopulations, although the estimates have not been validated sufficiently by actual measurements, and it is not clear whether the magnitude of differences in deposition attributable to the refinements are significant compared with the substantial magnitude of variability among subjects having similar characteristics. Models for extrapolating PM deposition and clearance between humans and rats have been refined (Miller, 2000; Winter-Sorkina and Cassee 2002), but extrapolation models for other species have advanced little.

Understanding of the deposition and fate of ultrafine PM has improved but is still inadequate. Even within the ultrafine size range (nominally 100 nanometers [nm] and less in diameter), there are size-related variations in alveolar deposition. Particles up to of 20 nm, however, are deposited with a much greater efficiency in the alveolar region than are fine and coarse particles (ICRP 1994). Although ultrafine PM can reach the deep lung, the alveolar deposition fraction is dependent on specific PM size and breathing pattern, and the ultrafine PM fraction is not always greater than that of fine PM. An understanding of the behavior of ultrafine PM after deposition, especially its transport to blood and other organs, has been enhanced somewhat. There is increased evidence for systemic transport of poorly soluble ultrafine PM (Oberdörster et al. 2002), but the lack of quantitative data does not yet allow the modeling of organ doses received by transport.

There have been no reports of the fate of the nonsolid organic condensate ultrafine PM, which constitutes a significant portion of the ultrafine population near combustion sources, particularly motor vehicle sources.

What Remains To Be Done?

Although expenditures related to dosimetry have been small, progress has been made in understanding particle deposition in the respiratory tracts of persons with preexisting respiratory disease. The greater deposition and the heterogeneity of deposition in abnormal lungs suggest one possible mechanistic basis for an increased susceptibility of persons with underlying lung disease to inhaled particles. Uncertainties remain on potential differences in fractional and regional deposition between older subjects and young adults and on the rates of translocation of PM to non-respiratory organs. Clearance has been less well-studied than deposition, and the effects of gender, age, and respiratory abnormalities on clearance remain largely uncharacterized. The committee's review showed numerous remaining gaps related to specific fractions of particles, especially ultrafine particles. More information on dosimetry in animal models of human disease is needed to facilitate extrapolation of findings from these models to humans.

RESEARCH TOPIC 7. COMBINED EFFECTS OF PARTICULATE MATTER AND GASEOUS COPOLLUTANTS

How can the effects of particulate matter be disentangled from the effects of other pollutants? How can the effects of long-term exposure to particulate matter and other pollutants be better understood?

Introduction

This research topic addresses the independence of the effects of PM on health—that is, whether the effects of PM depend on or are modulated by the presence of other pollutants, particularly the gaseous copollutants widely present in ambient air. The current approach to regulating the six criteria pollutants assumes that causal effects of each pollutant on health are

independent and that reductions of the concentrations of each will have a benefit for public health. To the degree that interactions among components of mixtures play a role in determining risk, policy implications of such interactions could be substantial. To establish the evidence base needed for the PM NAAQS, whether using experimental (for example, toxicological) or observational (epidemiological) approaches, researchers attempt to estimate an independent effect of PM on health, even though particles are part of a complex pollution mixture. The committee acknowledges that such approaches are likely to oversimplify the underlying biological processes and how the mixture of air pollutants that is inhaled adversely affects health. A finding that the effect of particles depends on the concentration of another pollutant—that is, "effect modification"—would have implications for setting NAAQS independently for the various criteria pollutants.

What Has Been Learned?

The more recent epidemiological and toxicological studies of PM and health provide clear evidence for an independent effect of PM in increasing risk for several adverse health outcomes. The evidence is less certain as to whether the effect of PM on these health outcomes depends on other pollutants. The subject is complicated by the possibility that there are different patterns of risk modification for different health outcomes. At the population level, time-series studies link levels of particles to mortality and hospitalization rates, after adjustment for other pollutants, particularly for cardiovascular diseases and COPD. In the multicity studies, other pollutants were explored as one determinant of the geographic heterogeneity in the risks associated with PM.

Researchers have assessed effect modification in a number of the time-series studies, including the U.S. National Morbidity, Mortality, and Air Pollution Study (NMMAPS) (Samet et al. 2000a, b) and the European (APHEA) study (Katsouyanni et al. 2001). The introduction of multiple pollutants into models beyond the index of PM tends to reduce the effect of PM, reflecting the intercorrelations of the other pollutants with PM (Samet et al. 2000c). In general, inclusion of interaction terms in models has not provided strong evidence for effect modification, aside from the occasional finding of a statistically significant interaction term, which may represent a type I statistical error resulting in a false rejection of the null hypothesis (Moolgavkar 2000). Unfortunately, the tests for interaction generally have

low statistical power, and their interpretation is further complicated by measurement error, which differs across pollutants.

Cardiovascular effects that might be considered as precursors of coronary events, albeit at high exposure concentrations, have been seen in animals (Godleski et al 2000). In these studies, particles with different characteristics appear to have different effects; however, there has been no clear indication of effect modification by other pollutants in animal studies in those few instances in which measurements of pollutant gases were also made.

Another approach to addressing the combined effects of PM and other pollutants is to relate health risks to indicators of source contributions to ambient air pollution, rather than using specific pollutant concentrations. The purpose of such studies is to identify sources, which might be of interest from a control strategy, but without specific consideration of the concentrations of specific components. That approach would not allow the disentanglement of effects to the various pollution components. For example, a number of recent investigations of childhood respiratory health used proximity to a major roadway as the principal exposure measure, focusing these studies on vehicle exhaust rather than its specific components. Those that assessed long-term effects suggested that both particles and gases appear to be related to excess morbidity, but few of these studies actually measured the components of the mixtures being assessed. In more recent analyses of acute morbidity and mortality, European and Canadian studies suggested that the effects of mobile-source pollutants are dominant over those of stationary-source pollutants; however, the pollutants measured (CO and NO_2) have been interpreted as potential surrogates for motor vehicle emissions (Touloumi et al. 1997; Roorda-Knape et al. 1998; Burnett et al. 2000). In other studies in areas where diesel exhaust is not dominant (such as Los Angeles), traffic-related pollution was associated with symptoms and respiratory effects in children, (Peters et al. 1999a,b).

The committee identified few studies that assessed long-term effects of particulate pollutants and modification of these effects by other pollutants. Those that were reported included cross-sectional assessments of symptoms and pulmonary function attributed to current or recent exposures and assumed to be applicable to lifetime exposure, actual measures of change in pulmonary function over a relative short term (3 years) of monitored exposure (Frischer et al. 1999), and detailed repeated evaluations for up to 20 years (Abbey et al. 1999). Most of these studies found excess rates of health-related parameters among people exposed to higher concentrations of particles. As part of mixtures, the other pollutants were not consistently measured or tested for their specific or combined effects. In humans ex-

posed to concentrated ambient particles (CAPs) plus O_3, high-resolution vascular ultrasonography showed increased brachial artery vasoconstriction as compared with that from filtered air (Brook et al. 2002). However, the partitioning of effects into those caused by components of the mixture has been difficult.

In carrying out experimental studies intended to replicate exposures to the complex mixtures that are found outdoors, replicating and characterizing the mixtures are difficult, as in epidemiological studies directed at exposures to outdoor air pollution. Most of the studies involved only PM and another pollutant and thus do not replicate the typical exposures of people. Experiments have been carried out that use ambient particles to which specific concentrations of an additional pollutant were added (Brook et al. 2002). Generally, exposures to particles and gases are given sequentially rather than simultaneously. Some of the more recent studies incorporated concentrated ambient particles (CAPs) (Kobzik et al. 2001). In older animals, greater effects were noted when O_3 was combined with PM_{10}. Exposures to diesel-generated particles with and without O_3 exposure have been used in chronic exposure studies of rats. However, even in these studies the characterization of exposure remains incomplete. Mechanistic studies of complex mixtures in laboratory animal studies have yielded results consistent with the findings of epidemiological studies, particularly as related to cardiovascular and respiratory findings. Similar changes in heart rate variability have been noted in compromised animal models as in some of the human studies.

What Remains To Be Done?

The committee's review found little new direct evidence related to topic 7, although the newer observational studies have continued to demonstrate an independent effect of particles that is robust to statistical adjustment for other pollutants. In its general review, the committee noted that assessments of effect modification in the epidemiological studies have provided little evidence that the effect of PM varies strongly with other major pollutants in ambient air. Interpretation of such analyses is complicated by the secondary nature of some PM, because both nitrogen oxides and sulfur oxides contribute to PM mass. Toxicological research, although limited, provides generally consistent findings. The committee considers that further research is needed to address topic 7, while acknowledging the challenges in carrying out such studies, whether based in observation or experiment. Effect modification of PM by other pollutants, particularly

ozone, can be more powerfully explored in planned larger studies, such as extensions of the NMMAPS approach. Better characterization of the mixtures contained in source-oriented exposure studies would make such studies more valuable. Ultimately, considering the entire mixture of air pollutants in the context of a multipollutant concept (see Chapter 5) will provide a fuller understanding of the contribution of the total atmosphere to adverse health effects. There may be undescribed synergisms among the mixture components that give the mixture greater risk than would be anticipated from the risks estimated for individual components.

RESEARCH TOPIC 8. SUSCEPTIBLE SUBPOPULATIONS

What subpopulations are at increased risk of adverse health outcomes from particulate matter?

Introduction

An understanding of susceptibility is critical to achieving the public health protection called for by the 1990 Amendments of the Clean Air Act, which extended protection against adverse health effects beyond the general population to especially susceptible subpopulations. The population as a whole is considered heterogeneous in its susceptibility to inhaled pollutants, including particles. However, diverse characteristics that may increase susceptibility to adverse health effects from inhaled PM include age (infants and older adults), the presence of underlying disease (chronic heart and lung diseases), altered deposition and clearance (morphological and physiological changes in the respiratory tract), activities that increase lung dose (for example, work or exercise outdoors), and exposures to other inhaled pollutants that might also adversely affect health (for example, airborne dust or fiber exposures in substandard housing). Research related to this topic addresses whether these or other factors increase susceptible individuals' responses to PM.

What Has Been Learned?

New knowledge about PM health effects in susceptible subpopulations has been developed in the past 5 years. Results from animal models and

clinical studies have reinforced epidemiological findings for susceptible subpopulations, increasing the coherence of the body of available evidence. Many of the epidemiological studies conducted in this period focused on children or older adults. Other epidemiological studies focused on people with asthma, COPD, or cardiovascular disorders. Controlled clinical and experimental animal studies examined responses to PM in people with airway diseases and animal models with compromised pulmonary and cardiovascular systems. However, there is growing recognition that the subpopulations who are most susceptible to PM exposures and the factors related to increased health risks are more numerous and diverse than once thought.

Recent research has confirmed previously observed adverse health effects and identified new ones. Some of the results, particularly on cardiovascular health effects and for older adults and people with asthma, have increased confidence in the prior findings. Results that were reported include the following:

- PM exacerbates existing asthma conditions among children and adults.
- Acute respiratory infections appear to compound adverse cardiovascular effects following PM exposures.
- Cardiovascular and respiratory effects in susceptible and general populations continue to be the health responses of greatest concern in relationship to PM exposures.

Since 1997, the number of studies examining the health effects of air pollution on children has increased substantially. The majority of these studies focused on the effects of PM and, in several cases, copollutants on the health of children with moderate to severe asthma. Taken as a whole, these studies confirm the findings of earlier studies regarding the adverse health effects of air pollution in general and of PM in particular on children's respiratory health. The studies are particularly compelling regarding the adverse effects of fine particles and possibly coarse particles as well on the exacerbation of preexisting illness in children with asthma (Norris et al. 1999; Timonen and Pekkanen 1997; Vedal et al. 1998). These results are similar to those reported for adults with asthma (Burnett et al. 1999; Sheppard et al. 1999).

Studies in dogs and rodents have been consistent with human research results. Aged rodents have been found to be more susceptible than young rodents to PM exposures, and infections are additional risk factors for adverse health outcomes in these animals (Elder et al. 2000a, b). These

findings are consistent with recent research results for older adults with preexisting cardiovascular disease (Zanobetti et al. 2000).

Both epidemiological and toxicological studies have identified and confirmed cardiovascular and respiratory effects as outcomes of concern in susceptible individuals. Although study results are not always consistent for lung-function measures, hospitalization, or mortality, decreased heart rate variability (HRV) has been reported in association with changes in $PM_{2.5}$ (Liao et al. 1999; Devlin et al. 2003). Similarly, cardiovascular effects, including changes in HRV following exposure of laboratory animals (dogs with coronary ischemia and hypertensive rats) to CAPs, have been reported (Godleski et al. 2000; Kodavanti et al. 2000).

There have been several new findings relevant to susceptible subpopulations. Research results show that following PM exposures, the following effects can occur:

- Persons with diabetes might be at increased risk for adverse health effects, including increased mortality.
- Intrauterine growth rates and newborn birth weights might be reduced by maternal PM exposures.
- Patients with asthma or COPD have greater deposition of inhaled fine and ultrafine PM, resulting in higher doses and related risks.
- Older adults experience adverse cardiac physiological changes.
- Older adults show hematological changes (for example, changes in blood coagulation factors).
- Dogs with coronary occlusion and hypertensive rats demonstrate adverse cardiac and vascular impacts.

One of the more surprising new findings is that persons with diabetes are at greater risk from PM exposures compared with the general population. The compromised cardiovascular condition of many with diabetes might be a key factor in this association. The studies that reported increased mortality among exposed persons with diabetes merit additional investigation (Goldberg et al. 2000; Zanobetti and Schwartz 2001).

Another major finding is the greater deposition of fine and ultrafine particles in the respiratory tracts of persons with asthma similar to what was earlier found in COPD patients (Anderson et al. 1990; Chalupa et al. 2002). Such increased deposition may contribute to the increased susceptibility of these subpopulations.

A few studies reported associations of maternal PM exposure and reduced intrauterine growth rates and low birth weight among the mothers' newborns (Pereira et al. 1998; Rogers et al. 2000). However, studies of

infant health outcomes, especially related to maternal environmental exposures, are difficult to conduct and must address numerous sources of confounding and potential uncertainty. These initial findings deserve further study.

Increased hospitalization rates among older adults with underlying cardiovascular disease have been associated with PM exposures and acute respiratory infections (Zanobetti et al. 2000). These results are consistent with the findings of increased susceptibility of aged rodents with infections, as noted above (Elder et al. 2000b, 2002).

Socioeconomic status has also been shown to modify the association between particulate air pollution and mortality. Krewski et al. (2000) showed that mortality associated with long-term exposure to particulate air pollution decreases with increasing educational attainment. Limited evidence of a similar modifying effect of socioeconomic status was also shown in time-series studies of air pollution and mortality (Villeneuve et al. 2003).

What Remains To Be Done?

Despite the recent advances in knowledge, substantial uncertainties still need to be addressed concerning susceptible subpopulations. New methods have to be developed for this purpose, as described in Appendix C.

To create the knowledge needed to understand the adverse effects of PM on susceptible subpopulations, research should more effectively address different scales of exposure (from short-term, peak to chronic exposures), characteristics of exposure (for example, deposition and disposition of fine and ultrafine particles in the respiratory tract), cellular and molecular mechanisms, the range of potential adverse health effects (for example, development of disease and organ dysfunction, neurotoxic and extrapulmonary effects, and life-shortening), and potential effect modifiers (for example, preexisting disease including infections). Current concerns focus on whether chronic PM exposures relate to the development of disease and organ dysfunction, the extent to which ultrafine particles of approximately 20 nm induce adverse effects in patients with asthma or COPD and the magnitude of life-shortening from PM exposures.

In addition, study methodologies should be improved. Important needs include the validation of animal models and demonstration of the relevance of these models, especially for mimicking compromised organ functions found in susceptible human subpopulations. In epidemiological studies, groups of people studied often include individuals at very different

points of physiological development (such as children ages 0-14) (Snodgrass 1992; Mennella and Beauchamp 1992; Burri 1997; Pinkerton and and Joad 2000; Mathieu-Nolf 2002) or with a wide range of health conditions (especially adults over age 65). Typically, such data are handled at the group level, with relatively little consideration of characteristics of the group members that might further determine susceptibility. Although such aggregation may make a study more manageable or improve statistical power, opportunities to examine adverse health effects among more specific subpopulations are lost. With the number of large-scale studies now available, it may be possible to combine and analyze data for key subpopulations using meta-analysis or other techniques, thereby capturing insights that might otherwise be lost.

RESEARCH TOPIC 9. MECHANISMS OF INJURY

What are the underlying mechanisms (local pulmonary and systemic) that can explain the epidemiological findings of mortality and morbidity associated with exposure to ambient particulate matter?

Introduction

This topic refers broadly to research on mechanisms that underlie the associations of PM with health outcomes. The sweep of relevant research is broad and extends well beyond research on PM specifically. Of necessity, the committee's review has been selective, focusing on some of the most relevant findings since its first report.

When the committee's first report was published, little work could be cited that indicated potential mechanisms underlying the epidemiological findings of increased mortality and morbidity. The emphasis up until that time was on pulmonary mechanics and pulmonary defense mechanisms. The exposure materials were primarily secondary inorganic aerosols, including nitrates and sulfates with a few studies addressing carcinogenicity of diesel exhaust. The studies were largely negative in not showing effects except at high concentrations with some suggestion of increased susceptibility of adolescents with asthma. In addition, given the emerging findings from the epidemiological studies of increased risk for cardiovascular effects from PM exposure, there was a paucity of toxicological studies looking at possible mechanisms. Firmer conclusions for policy implications appeared

to be dependent on finding underlying mechanisms that would explain why cardiac effects could be anticipated. In response to the lack of a mechanistic underpinning in support of the epidemiological findings, the committee called for an ambitious agenda of carefully designed mechanistically based controlled exposure studies.

Several categories of studies were listed, using three approaches: (1) controlled clinical sites, (2) animal toxicological studies, and (3) in vitro studies.

What Has Been Learned?

These approaches have provided new insights into mechanisms. A major gain in mechanistic understanding since 1997 involves an expansion in focus to cardiovascular and subtler pulmonary responses. In the past, investigations tended to focus on the respiratory tract as both the portal of entry for particles and the site where effects were manifest. It is increasingly recognized that the respiratory tract may serve as the portal of entry of particles that are related to health effects manifest in organs and tissue remote from the respiratory tract. Using existing epidemiological and experimental data, an interdisciplinary workshop suggested that mechanistic considerations should focus on alterations in the autonomic nervous system; ischemic responses in the myocardium; chemical effects on ion channel function in myocardial cells; and inflammatory responses triggering endothelial dysfunction, atherosclerosis, and thrombosis (Utell et al. 2002). In fact, recent studies in humans and animals have demonstrated alterations in the autonomic nervous system, cardiac repolarization, and endothelial responses in response to particles (Utell et al. 2002). Descriptive findings of electrocardiogram changes and vascular end points confirmed a role of ambient PM and surrogate particles on extrapulmonary organ functions. As a basic mechanism for these effects, local and systemic oxidative stress responses were identified, as was a central role of oxidative stress in response using in vitro models.

Together with the shift in mechanistic focus, there were appreciable changes in the experimental systems used. For example, animal models used in recent years have changed appreciably, with more given to potentially susceptible animals defined both by age and disease conditions that more realistically reflect human disease. Chronic exposures of these animals have not been carried out mainly because of the practicality of sustaining colonies of animals for long periods. There has been an increased use of real-world particles, including CAPs and fine and ultrafine particles.

In contrast to earlier approaches involving exploration of mechanisms in highly focused studies, more integrative approaches are now being taken so that data from different disciplines can be integrated in a more cohesive consideration of biological plausibility. The result has been the development of hypotheses that focus on specific areas, including (1) inflammation, both pulmonary and systemic, with perhaps a key role played by reactive oxygen species (ROS); (2) alteration in immune competence; and (3) autonomic nervous system dysfunction. Although these mechanisms are often considered individually, they are undoubtedly interrelated. Reviews of each topic are presented below.

Inflammation and Immunity

The presence of an inflammatory response is an important issue, because inflammation may induce systemic effects, including an acute-phase response with increased blood viscosity and coagulability, and possibly an increased risk for myocardial infarction in persons with coronary artery disease. In chronic respiratory diseases, such as asthma and COPD, inflammation is also a key pathophysiological feature. Chronic, repeated inflammatory changes of the airways may result in airway remodeling that leads to irreversible lung disease. Thus, inflammation may be involved in both acute and chronic effects.

Recent controlled-exposure studies in humans indicate that several types of particles can induce an inflammatory response. Studies using CAPs, laboratory-generated carbonaceous ultrafine particles, and diesel particles have all provided evidence for effects on pulmonary or systemic inflammatory markers. For example, levels of cytokines, chemokines, and adhesion molecules following particle exposures in healthy humans have been altered in blood (Salvi et al. 1999; Ghio et al. 2000a; Frampton et al. 2001). These soluble molecules play an important role in blood-cell recruitment to atherosclerotic lesions and inflamed airways, suggesting that exposure to either CAPs or ultrafine particles may initiate endothelial and leukocyte activation, a key initial step in leukocyte recruitment.

Similarly, studies in normal dogs exposed to CAPs from Boston's air by inhalation showed increases in pulmonary inflammation measured by bronchoalveolar lavage and in circulating blood neutrophils related to increases in specific ambient particle components (Clarke et al. 2000). Another possible consequence of exposure is increased susceptibility to acute respiratory infection. *Streptococcus pneumoniae*-infected rats ex-

posed to PM demonstrated increased pulmonary burdens of bacteria, circulating white blood cells, extent of pneumococcal-associated lung lesions, and incidence of bacteremia (Zelikoff et al. 1999). Subsequent studies implicated the iron content in mediating these effects. These findings suggest that PM, especially the soluble iron component, affects the host immune response during pulmonary infection and helps to explain some epidemiological observations.

Cardiovascular Effects

There is growing clinical and epidemiological evidence that ambient air pollution can precipitate acute cardiac events, such as angina pectoris, cardiac arrhythmias, and myocardial infarction, with the majority of excess PM-related deaths attributable to cardiovascular disease. Clinical studies of young and older subjects exposed to CAPs have shown reductions in heart rate variability (HRV) and increases in blood fibrinogen levels (Devlin et al. 2000, 2003). In another study, cardiac repolarization and responses of the parasympathetic nervous system were blunted during recovery from exercise immediately after exposure to ultrafine particles (Frampton 2001; Frampton et al. 2002). Similarly, animal studies are linking exposure to PM with changes in cardiac function, including induction of arrhythmias and an increased incidence of myocardial infarction. Inhaled PM exacerbated ischemia in a model of coronary artery occlusion in conscious dogs. Exposure to CAPs significantly increased peak ST-segment elevation during a 5-minute coronary artery occlusion (Wellenius et al. 2003).

Investigators have focused on systemic inflammation and alterations in vascular endothelial function to explain these cardiac phenomena. Humans exposed to ambient particles showed increased blood levels of endothelins, which affect vascular tone and endothelial function (Vincent et al. 2001a,b), and altered vascular tone assessed by an ultrasound technique (Brook et al. 2002). In summary, an impressive array of findings from in vitro, animal, and human studies have provided a much more robust understanding of the potential mechanisms responsible for particle-induced cardiovascular events. Although a definitive mechanism has not been established to explain either increases in cardiac arrhythmias or myocardial ischemia, it has become clear that particles are capable of inducing many of the intermediate steps that are linked to adverse cardiac outcomes.

Oxidative Stress

Recent work has focused on oxidative stress as an underlying mechanism relevant to pulmonary, cardiovascular, and other systemic effects. PM generates ROS, which provide pro-inflammatory stimuli to bronchial epithelial cells and macrophages. These cellular targets release cytokines and chemokines, enhancing the response to allergens. PM might therefore act as an adjuvant that strengthens the response of the immune system to environmental allergens. Hallmarks of allergic inflammation include increased immunoglobulin E (IgE) production, eosinophilic bronchial inflammation, airway hyperresponsiveness, and increases of NO in exhaled air. Diesel exhaust particles (DEP) markedly enhanced the antibody response and lipid peroxidation in allergic animals, while pretreatment with an antioxidant minimized the response (Whitekus et al. 2002). These findings are consistent with human nasal challenge studies supporting the role of DEP as an adjuvant in an already established allergic response, as well as in an exposure to neo-allergens. More recent studies found that diesel exhaust inhalation increases inflammatory markers (such as lung neutrophils and eosinophils) in healthy volunteers, supporting the hypothesis that diesel exhaust can worsen respiratory symptoms. DEP alone might augment levels of IgE, trigger eosinophil degranulation, stimulate release of various cytokines and chemokines, and stimulate the T_H2 pathway (Pandya et al. 2002). Taken together, these findings might be relevant in explaining the increased number and severity of asthma attacks related to acute or short-term increases in PM levels in an urban setting and could implicate DEP and other types of PM as factors in asthma exacerbations.

ROS associated with exposure to PM might play a role in cardiovascular effects. Quinones and other compounds that produce ROS might contribute to disease-related vascular dysfunction caused by PM exposure. That possibility could become particularly relevant as understanding of the role of PM in endothelial dysfunction expands and could further explain the mechanisms underlying cardiovascular events.

What Remains To Be Done?

Despite progress since 1997, uncertainties still exist in the scope and significance of experimental data in explaining the epidemiological findings on risks of PM. There are important limitations in the understanding of the relevance of mechanisms observed in animal and in in vitro systems for

humans. That is particularly the case in extrapolations from high-dose animal exposure to low-concentration human environmental exposure. Similar problems occur in understanding the relevance of mechanistic observations from nonphysiological exposure routes, such as instillation, to the normal inhalation route of pollutant exposure. The findings from the clinical, animal, and in vitro experimental work have often not included dose-response relationships. Such dose-response studies are an important element of confirming a mechanistic basis in support of the epidemiological findings. In addition, similar physiological, cellular, and molecular responses to PM in different species help to provide a mechanistic underpinning to the epidemiological observations.

To date, the mechanistic observations have been largely in the realm of physiological and cellular mechanisms. The molecular mechanistic basis for the observed health effects is yet to be explored but is a necessary approach in moving forward. This approach is likely to become increasingly important as the research community moves into the discipline of molecular epidemiology.

Another major uncertainty relates to the lack of the understanding of the relationships between the mechanisms responsible for acute versus chronic health effects. As focus shifts to findings from epidemiological studies on chronic health effects, a similar shift will be required of the mechanistic studies. At present, it is unclear how the mechanistic findings from acute health effects studies will relate to the mechanisms underlying chronic health effects.

Finally, much of the exploratory, hypothesis-generating research done to date has focused on identifying mechanisms. The next step is to more clearly understand mechanisms underlying exposure-response relationships, recognizing that it is likely that most mechanisms will have some element of exposure (dose) dependence. This issue is critical to understanding the relevance of the various mechanisms described in experimental systems to ambient PM concentrations typically encountered by people.

RESEARCH TOPIC 10. ANALYSIS AND MEASUREMENT

To what extent does the choice of statistical methods in the analysis of data from epidemiological studies influence estimates of health risks from exposures to particulate matter? Can existing methods be improved? What is the effect of measurement error and misclassification on estimates of the association between air pollution and health?

Statistical Analysis

Introduction

Statistical analysis of data is the basis for making inferences about the underlying relationship between health and air pollution from epidemiological data. The goal of this research topic is to develop appropriate methods to analyze collected data and to understand the potential influences of these methods on the inferences that are made. Rapid developments in computing hardware and in statistical software have fostered the development and application of increasingly sophisticated statistical methods for analysis of large and complex epidemiological databases.

What Has Been Learned?

At the time of the committee's first report, several statistical models had been developed to analyze the relationship between daily health end points and daily air quality measures, which were widely used for analysis of time-series data related to morbidity and mortality. Other key issues, such as measurement error, harvesting,[1] and spatial analytical methods, had not yet been addressed rigorously but were recognized as methodological concerns in interpreting the findings of time-series studies. To some extent, the statistical literature addressed these issues generically, but they had not yet been applied to the type of data collected in health and air pollution epidemiological studies.

Since 1997, several new statistical methods have been introduced to analyze the temporal association between air quality measures and health. Because approaches to analysis varied widely among researchers, comparisons of findings across locations were complicated by the possibility that methodological differences in analytical methods, rather than biological differences in the effects of particles, contributed to differing levels of association across locations. The National Morbidity, Mortality and Air Pollution Study (NMMAPS) (Samet et al. 2000a,b) was a major effort designed partly to overcome that problem by applying the same methods to

[1]The term harvesting refers to the question of whether air pollution leads to the death of people who are highly susceptible and near death (and die a few days earlier than they would have with no air pollution exposure) or whether air pollution leads to the death of people who are not otherwise near death.

data from multiple locations. The NMMAPS approach used data from multiple cities across the United State. The cities were selected solely on the basis of size, thereby avoiding bias from picking a particular city and assuring representativeness of the findings. Work by the NMMAPS investigators led to the identification of a problem in the application of the SPlus software's GAM (generalized additive model) function as applied to air pollution time-series data (Dominici et al. 2002). That finding, along with more detailed assessment of the methods applied to time-series data throughout the 1990s, indicated other methodological issues that had a potential impact on the effect estimates and their standard errors. The magnitude of the bias varied in a complex fashion with underlying modeling assumptions and the data structure of particular locations. Further examination of those estimates (Ramsay et al. 2003a,b) indicated that the standard errors of the measures of association were systematically underestimated, resulting in the potential to increase the level of statistical significance.

Given the implication of those new findings with regard to the time-series studies, EPA slowed closure of its criteria document for PM and organized a framework for reanalysis of key data sets. In November 2002, EPA convened a workshop at which several investigators presented their results after applying several methods to the same data sets. For some data sets, the results appeared to be robust across several alternative methods that were applied. In other cases, the results differed, sometimes to the point that results would be statistically significant under one method but not under another. The differences occurred not only within the widely used GAM framework but also between GAM and other approaches, such as the generalized linear model (GLM), and among assumptions used within the GLM framework (HEI 2003).

To date, there is no consensus about which analytical method is "correct." Researchers are confronted with the need to estimate relatively small associations in the presence of potential confounding by weather and seasonality. Until the implications of the alternative analytical approaches are fully understood and until there is some scientific consensus about the appropriate method to use, researchers must explore the sensitivity of results to alternative modeling approaches (Sarnat et al. 2000). A further source of sensitivity has come with the increasing use of the case-crossover design, an alternative individual-level approach to assessing exposure-response on short time frames. The optimal uses of this design are still being explored. One recent report compared the results from a case-crossover

analysis with the more widely used time-series methods (Fung et al. 2003).

The time-series models inherently make assumptions about the appropriate time domain for air quality data to be related to health studies. Some recent studies considered continuous air quality data and suggested alternative exposure metrics (exposure lengths less than 1 day or peak exposures). Distributed lags have also been introduced to estimate the temporal relationship between exposure and response in more detail. Several studies considered the issue of mortality displacement or harvesting, using various analytical strategies. The majority of these studies found that a significant number of deaths cannot be attributed to harvesting alone (Zeger et al. 1999; Schwartz 2000; Dominici et al. 2000), and the findings of several others suggested that harvesting can be substantial (Smith et al. 1999; Murray and Nelson 2000).

Significant methodological improvements have been made in other areas as well. The identification and treatment of spatial autocorrelation (an interdependence between variables in different locations) have been addressed in studies that examined patterns in health and air quality indices in several geographic areas (Krewski et al. 2000; Burnett et al. 2001). However, the effects of concurvity noted in time-series studies (Ramsey et al. 2003a) are also apparent in spatial analyses (Ramsey et al. 2003b). New methods have been applied that allow the combinations of results across several studies, for example, in several cities in which a common methodology was applied.

What Remains To Be Done?

Although the committee's previous reports had found substantial progress related to this topic, recent findings on the sensitivity of time-series results to modeling approaches are an indication that further methodological research is needed. Time-series studies are likely to remain important for estimating the health effects of air pollution on populations, and a more complete understanding of the implications of modeling approaches is needed. Additionally, the issue of harvesting or mortality displacement needs further investigation, and the seeming discrepancy between the strength of associations of PM with mortality in the daily time-series studies and the cohort studies needs explanation.

Measurement Error

Introduction

Measurement error is inherent in most studies of environmental factors and disease, potentially affecting exposures of interest, confounding and modifying factors, and outcomes. In epidemiological studies, the individual's exposure to pollutants of concern cannot be known for all relevant time averages. The difference between the actual exposure and the measured exposure is known as measurement error. Generally, three components are in this measure: errors due to instrument error; errors due to the unrepresentativeness of an air quality monitor; errors due to differences between the monitored pollution measures and the average actual exposure. There is substantial statistical and epidemiological literature on measurement error, but the committee identified a number of issues specific to assessing exposures to PM and the health consequences of these exposures. A particular concern is the use of central-site monitoring data as an indicator of personal exposure in the time-series studies.

What Has Been Learned?

Zeger et al. (2000) developed a framework for measurement error in the context of air pollution epidemiological studies. They showed that under a wide range of circumstances, measurement error might result in underestimates of the association between air pollution variables and risk for adverse health effects. In recent years, more data have become available to examine the statistical properties of measurement error. They include data on the statistical distributions of the differences between personal exposures to a variety of pollutants and ambient measures for the same pollutants (Sarnat et al. 2001). Other studies (Ito et al. 2001) have tried to characterize the geographic variability in pollution measures. These data enable some validation of the statistical assumptions made in the developed frameworks and will provide input data for models that will estimate the impacts of measurement error. Because data will be available for several pollutants, it will be important to address this problem in a multipollutant context. These analyses might be limited by the lack of reliable data for short-term personal exposures to CO. Mallick et al. (2002) explored the use of methods for adjusting for exposure measurement error in the Cox regression model used to describe mortality associated with long-term exposure to PM air pollution.

There are many issues that influence an understanding of the health risks associated with particles. Research is continuing on these issues; however some of them are associated with considerable uncertainty. Some are addressed elsewhere in this section (for example, model selection, measurement error) and in this document (for example, differential toxicity of different particulate components, impacts of simultaneous exposure to copollutants); however, there have been no general framework and methodology to consider the quantitative impact of the totality of these uncertainties. Such a framework with corresponding methodology could not only prove useful in identifying the most critical uncertainties but could also be used to set priorities.

What Remains To Be Done?

The limited application of the framework developed for measurement error suggests that measurement error per se will not negate the positive associations found between air pollution and health effects. More precise estimates of the magnitudes and statistical distributions of measurement error need to be incorporated into multipollutant models to provide more reliable quantitative estimates of the impact of measurement error and of the relative importance of the various pollutants on health impacts. Greater consideration of this issue will give more credence to risk assessments used to support regulatory decisions.

Frameworks have been developed which consider many of the components which influence an understanding of the PM-health relationship, and sensitivity analyses have been undertaken for some of these components. A recent NRC report (*Estimating the Public Health Benefits of Proposed Air Pollution Regulations* [NRC 2002]) addressed this issue and recommended some possible approaches, including Monte Carlo analysis and decision analytic tools.

SUMMARY

To date, the greatest measurable gains have been made on the topics with a narrower scope, such as exposure assessment and dosimetry. Substantial new evidence on exposure to particles has been reported, and there is now an enhanced understanding of the determinants of personal exposures to particles in ambient air (topic 1). Substantial progress has been made in assessing PM exposures of healthy individuals as well as suscepti-

ble subpopulations. Equipment and protocols for this purpose were available before the committee's first report, and the new funding made available for this topic led to a clear advance in the available evidence. Although monitoring methods are being developed to assess exposures of susceptible subpopulations to hazardous PM components (topic 2), more substantial advances are needed in assessing the components themselves (topic 5) before fully implementing topic 2.

Topic 6, dosimetry of particles, is of narrow scope, and an understanding of particle dosimetry in the lung had already been well-established. Dosimetry models have been enhanced in the past few years, although not yet sufficiently developed for those with chronic heart and lung disease.

Research methods have been further elaborated, and insights have been gained into the statistical modeling of data on air pollution and health (topic 10). Substantial methodological research has yielded new analytical strategies and an enhanced understanding of several issues, including measurement error and possibly mortality displacement. Methods have been described for combining large amounts of data to detect the effects of air pollution with greater sensitivity. In addition, new methodological issues in time-series analyses have been identified and solutions proposed.

Regarding the combined effects of PM and gaseous copollutants (topic 7), epidemiological and toxicological research has provided little indication that PM effects vary with levels of other major pollutants in ambient air; however, much research on topic 7 is needed. New knowledge about PM health effects in susceptible subpopulations (topic 8) has been developed in the past 5 years. Despite such advances in knowledge, substantial uncertainties still need to be addressed concerning those subpopulations.

Finally, a critical information gap, which is related to the characteristics of particles determining risks to health and the sources of more hazardous particles, remains largely unaddressed. An understanding of health risks in relation to particle characteristics lies largely in the domains of topics 5 and 9, and information on their sources and concentrations is the focus of topics 3 and 4. Progress on topic 5 has been slow, despite its central place in moving forward on the committee's agenda. In the final chapters of this report, we offer recommendations on how to move forward more quickly on this topic.

4

Looking Across the Research Topics

INTRODUCTION

In the preceding chapter, the committee provided its review of progress on research topics 1-10.[1] This new information will help to reduce uncertainties in the framework for assessing the public health risks from emissions of airborne particles and their gaseous precursors. The committee's research portfolio is for research to investigate particle toxicity, assess human exposures, examine biological mechanisms, identify particle sources, and develop tools needed to formulate effective control strategies. Research findings would constitute the scientific basis for assessing the burden of disease associated with specific particle categories and for evaluating the potential effectiveness of various control strategies for protecting public health. The committee has given similar emphasis to the 10 topics, recognizing that all need to be addressed to have an evidence-grounded approach to controlling particulate air pollution.

As the context for particulate matter (PM) research has evolved, five cross-cutting issues have emerged: (1) an increasing number of adverse health outcomes associated with PM and the related susceptible subpopulations; (2) particle toxicity in relation to different particle characteristics and emission-source types; (3) increasing emphasis on exposure-dose-response relationships; (4) consideration of particle health effects within the broader context of the myriad other pollutants present in the ambient air; and (5) consideration of the implications for setting and implementing the PM NAAQS.

[1]A list of the 10 topics is provided in Box 1-1 in Chapter 1.

HEALTH OUTCOMES AND SUSCEPTIBLE SUBPOPULATIONS

Research results under the topics of outdoor measures versus actual human exposures (topic 1), dosimetry (topic 6), combined effects of PM and gaseous pollutants (topic 7), susceptible subpopulations (topic 8), and mechanisms of injury (topic 9) indicate a broadening scope of health concerns since the committee's 1998 report. At that time, emphasis was largely placed on total morbidity and mortality from respiratory causes, such as exacerbation of chronic respiratory diseases, including chronic obstructive pulmonary disease (COPD) and asthma, and the respiratory health of children. Subsequently, the list of particle-related health outcomes was broadened and now includes several adverse cardiac outcomes, such as changes in heart rate variability, cardiac arrhythmias, ischemic events, and congestive heart failure, as well as reproductive outcomes. Although findings on several of these outcomes remain preliminary and inconsistent, the interest in investigating these outcomes and exploring new ones has grown.

Individuals with chronic lung disease have long been considered to be at increased risk for adverse effects of air pollution, based on compromised physiological reserve capacity. Dosimetry studies show that such persons have enhanced deposition of particles in the central lung, possibly contributing to increased risk. The expanded scope of health studies now includes investigation of other potentially susceptible subpopulations, such as individuals with coronary heart disease or diabetes.

New studies were conducted in many U.S. cities to better understand the relationship between outdoor measures of PM and actual human exposures. Panels of susceptible subpopulations were investigated, including people with COPD or coronary heart disease, older adults, children, and people with asthma. These studies found that there were varying degrees of association between personal exposures and ambient concentrations for the measured individuals, with almost half of the associations being nonsignificant (see Chapter 3). More important, studies conducted in the eastern United States showed little difference in $PM_{2.5}$ exposures among the different investigated cohorts, despite their differing time-activity patterns. Future research studies should be conducted to investigate populations at high risk residing near source-dominated environments. Progress in air quality model development and testing (topic 4) and characterization of emission sources (topic 3) will facilitate greater accuracy in the identification of populations exposed to high PM concentrations.

ASSESSING HAZARDOUS PARTICULATE MATTER COMPONENTS

Ambient particles contain a large spectrum of individual compounds. Research findings from the Supersites Program and other atmospheric characterization studies have elegantly demonstrated the complexity of ambient particle characteristics. Research to assess hazardous PM components (topic 5) seeks to understand the comparative toxicity of particles in relation to their specific characteristics (for example, size or composition). Such information is helpful for the development of effective controls on emission sources to protect public health.

The current National Ambient Air Quality Standards (NAAQS) for PM are based on size and mass and assume that all particles have the same toxicity per unit mass irrespective of chemical composition. In the committee's judgment, that assumption greatly oversimplifies complex biological phenomena that are influenced by PM and other pollutants. There are numerous physical and chemical characteristics of particles that are potentially relevant to their toxicity; however, to date, there is little information on the relationship between health outcomes and specific particle properties or source types.

Research to date has provided some new insights concerning particle characteristics and toxicity. For example, as discussed in Chapter 3, there are studies suggesting that health impacts of sulfate per se may not be proportional to their contribution to ambient PM mass. From the regulatory point of view, that is an important finding, because ammonium sulfate represents a significant fraction of PM, especially in the eastern United States, where it is the dominant component of secondary PM and is largely attributed to a small range of source types (for example, coal combustion). The toxicity of a range of particle components and sizes will need to be explored across the relevant health outcomes. Investigating the rest of PM components will be a challenging task, considering the complexity of PM as supported by numerous PM characterization studies (see Chapters 1 and 3); however, it is imperative that more progress be made in this area.

Without sufficiently compelling findings on the assessment of hazardous PM components, the committee's research agenda could stall, and the possibility of standards and control strategies that go beyond the current mass-based approach would be delayed. Further research on emission characterization, development and testing of air quality models, and exposure of individuals at greatest risk needs to be linked to and redirected by advances in research on the assessment of hazardous PM components. A

better understanding of particle toxicity will enable atmospheric scientists to focus their air quality models on particle types most critical to public health. An improved understanding of PM toxicity will help to develop air quality monitoring networks to support epidemiological studies investigating PM toxic components. New information on hazardous PM components would help to guide efforts to better understand the deposition and fate of relevant particles (topic 6). Research on biological mechanisms (topic 9) and identification of susceptible populations (topic 8) could be better enhanced by research accomplishments on topic 5. Findings from research on topic 5 will guide mechanistic studies, topic 9, to focus on specific toxic components or size fractions of PM. Integration of research across topics 5 and 9 should be further enhanced.

The slow pace of research on assessing the hazardous components of PM may reflect not just the difficulty of the scientific questions but also the limitations of the investigator-initiated, hypothesis-driven approach to carrying out systematic screening across the matrix of particle characteristics and health outcomes that is the foundation for topic 5. A large array of questions for investigation is defined when the diversity of possibly relevant particle characteristics is crossed with the broad range of potential health effects. This array has not been screened to identify the most plausible pairings of characteristics and effects. Instead, most investigators have pursued specific hypotheses, often with some justification, but leaving plausible alternatives unexplored and not attempting to systematically cover the full range of potential characteristics of interest. A much more systematic approach may need to be taken for future research to assess the hazardous components of this complex mixture called PM. New research and research management strategies may also be needed, as discussed in Chapter 6.

The committee considered the kind of evidence that would be informative for assessment of hazardous PM components. As emphasized previously, this topic does not have the simplifying and unrealistic objective of identifying single characteristics of particles that determine toxicity. Rather, the emphasis is on assessing the comparative toxicity, including exposure-dose-response relationships, of particles of differing characteristics and from different sources. Epidemiology and toxicology are two relevant and complementary research approaches for pursuing that objective. For either discipline, the ideal data might take the form given in Figure 4-1, which illustrates a comparative assessment of risk for particles of different compositions. Efforts to compare different types of PM are complicated by the possibility that the exposure-dose-response relationships for some types of PM and health effects may not be linear.

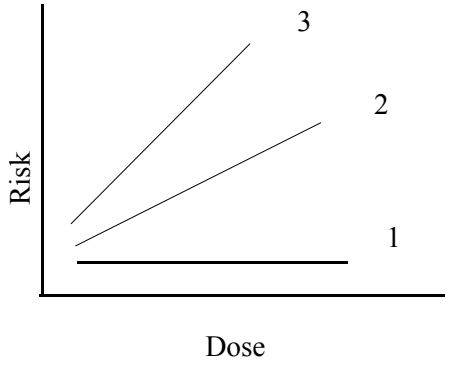

FIGURE 4-1 Illustrations of hypothetical evidence showing different slopes of dose-response for three particle types measured for the same exposure period. Idealized relationships are shown between health risk for a particular health endpoint and three types of particles (1, 2, and 3) that differ in metal content, for example. For the purpose of this illustration, linear relationships are depicted, but other shapes are possible, including non-linear responses and thresholds. The figure illustrates that for a given mass of inhaled particles, the level of risk may be substantially different, depending on the particle composition. A reduction in the mass of particle type 1 would result in little reduction in risk, and a reduction in the mass of particle types 2 or 3 would result in much more-pronounced reductions in risk. The shapes and relative positions of the three dose-response curves could likely be different for other health outcomes.

Epidemiologists approach the topic of assessing hazardous PM components by carrying out research across locations having particles with different characteristics or across time periods over which particle characteristics might differ. Multivariable models are the fundamental tool for attempting to gauge the comparative effects of exposures to different particle mixes. Additionally, in several epidemiological studies, data on particle composition have been used to develop source-surrogate exposure indicators, and in a larger number of studies, exposure to one source, on-road vehicle exhaust, has been studied. The category of source-oriented studies can provide data on relative toxicity. Toxicologists have compared the toxicity of particles having differing characteristics in the same bioassay system, but there is no standardization of such assays or of the doses at which they are applied. Findings may not be readily compared across studies as a result. Integrated epidemiological and toxicological approaches will be needed so that hypotheses can be mutually tested and findings cross-validated based on human observational and animal experimental data.

INCREASING EMPHASIS ON EXPOSURE-DOSE-RESPONSE RELATIONSHIPS

In the committee's view, emphasis should be shifted from research directed primarily at the question of whether particles are causing particular health effects to that of characterizing exposure-response or dose-response relationship—that is, what is the form of the quantitative relationship between exposure and risk for an outcome? This quantitative understanding can guide decisionmaking, offering a foundation for estimating the burden of morbidity and mortality caused by particles and comparing the benefits of alternative scenarios of air quality management. The design of research directed at characterizing dose-response relationships may differ from that directed at hazard identification. Information on dose-response relationships is particularly needed across a range of particle exposures relevant to those received by people at contemporary concentrations.

Knowledge of exposure-dose-response relationships is important to establishing the NAAQS for PM and implementing effective control strategies. Exposure-dose-response was viewed as the umbrella issue that included health-related research topics. During the past 6 years, research on these topics focused mainly on examining the causal association between PM exposure and increases in risks for adverse health effects. Very few of the studies using in vitro or laboratory animal models have included more than one exposure or dose level, limiting progress in characterizing exposure-response relationships. However, the research performed to date provides essential background information for conducting the next generation of research on population-based exposure-dose-response models, which are needed to evaluate the effectiveness of implementation plans.

The incorporation of approaches that will allow examination of exposure-dose-response relationships in in vitro and laboratory animal experiments will be particularly critical in further research evaluating the comparative toxicity (potency) of PM components. The strongest information base on exposure-response relationships for PM and other pollutants comes from some of the largescale epidemiological studies that have examined several PM metrics, such as PM_{10} or $PM_{2.5}$, and reported the results as an increase in adverse effects per 10 micrograms per cubic meter ($\mu g/m^3$) of the metric. The linear relationship between exposure and response has been supported by some detailed evaluations that have generally supported a monotonic increase in response associated with increased exposure. It is anticipated that future epidemiological studies can build on the toxicological findings and test the hypothesis that some specific PM components have potencies different from those observed for PM_{10}, $PM_{2.5}$,

or particles with aerodynamic diameters between 10 and 2.5 μm. In addition, epidemiological studies can benefit from future exposure studies of susceptible individuals to particles and other pollutants. Also, exposure studies will be necessary to inform epidemiological investigations about relationships among personal exposures to hazardous PM components and ambient concentrations for susceptible subpopulations and the general public.

MIXTURES AND COPOLLUTANTS

For some time, investigators have recognized that surrogates for "dirty air" have been derived from assessing one pollutant at a time, and possible health effects attributed to a single pollutant have often been used in part to make regulatory decisions. Over the past several years, scientists and regulators have been concerned about human exposure to air pollutant mixtures in settings other than specific occupational settings (topics 1 and 2). In addition, the recognition of a broader range of health impacts as being putatively related to ambient pollution raises the possibility that single pollutants might be acting together to increase risk through additive or synergistic mechanisms (topic 7).

Research findings on the combined effects of particles and gaseous copollutants (topic 7), susceptible populations (topic 8), mechanisms of injury (topic 9), and human exposures (topic 1) have implications that extend beyond PM alone. The finding of synergism between PM and other criteria pollutants, especially ozone, would have implications for the form of the NAAQS, which assumes independence of effects. For instance, clear evidence of synergism among the various pollutants for which NAAQS are set would provide a rationale for more integrated standards reflecting realistic atmospheric mixture exposures to populations at risk and the potential for overall mixture toxicity. A more detailed discussion on this topic is presented in Chapter 6.

There is overlap among some mechanisms and targets, such as activation of inflammatory cascades, that are considered to underlie the adverse effects of PM and certain gaseous pollutants (topic 9). Oxidative injury is another mechanism thought to have a role in lung injury by PM, ozone, and nitrogen oxides (topic 9). Thus, the insights gained from investigations of mechanisms of respiratory injury by PM may have wider applicability, although some pollutants have specific targets, for example, carbon monoxide and hemoglobin.

Recent reports on proximity to traffic and risks to health further support research directed more broadly at air pollution. Studies on the adverse health effects of air pollution on children with asthma and other populations residing in relatively close proximity to highly trafficked roadways underline the importance of identifying susceptible populations on the basis of exposure to high concentrations of air pollution (topics 1, 2, 3, and 4) and increased responsiveness to air pollution toxicity (topics 8 and 10). Additional studies on the exposure-response patterns of older subpopulations and patients with diabetes who appear to be susceptible to multiple pollutants further underline the importance of mixtures. To date, limited human health effects research has been conducted to apportion the effects of single pollutants coexisting with other pollutants in complex mixtures (topic 7). Similarly, only a few animal inhalation studies have used more than two pollutants in sequence or simultaneously, for example, concentrated ambient particles (CAPs) with carbon monoxide or ozone (topic 9). However, considering the complexity of exposures and the variety of potential responses to air pollutant mixtures, the paradigm of assigning effects to single pollutants should change.

NAAQS IMPLICATIONS

Setting NAAQS

Important remaining research needs are those that could affect the four elements of the NAAQS for PM, namely, the indicator, the averaging time, the numerical level of the indicator, and the statistical form of the standard. For control purposes, sources that should have priority for reduction need to be identified. Exposure assessment, emissions characterization, development and testing of air quality models, assessment of hazardous PM components, combined effects of PM and gaseous pollutants, and mechanisms of injury (topics 2, 3, 4, 5, 7, and 9) are particularly relevant. The current and all previous versions of the NAAQS for PM have been based primarily on human epidemiological data with support of data from other lines of research. The committee's review of current and ongoing research suggests that epidemiological evidence will remain central in setting the NAAQS, but enhanced mechanistic understanding could guide the choice of the indicator and averaging time.

NAAQS Implementation

More research is necessary for emissions characterization and air quality model testing and development to meet implementation deadlines (see Chapter 5). Measurements of source emission rates for PM and precursor gases as well as evaluation of models are needed, because states are in the process of developing state implementation plans for attaining PM NAAQS. To expedite progress on those topics, EPA should provide more guidance, leadership, and coordination among the groups carrying out this work, particularly those conducting emissions characterization (see Chapter 6).

Results of epidemiological research could provide greater information about those components of PM and air pollution that can most impact health. Future state implementation plans (SIPs), which are plans for reducing emissions so that an area can come into compliance with NAAQS, could therefore benefit from new and existing research in this area. Such information would enable SIPs to prioritize emission-control efforts starting with those sources contributing the greatest potential health impacts.

5

The Challenges Ahead for Particulate Matter Research

INTRODUCTION

In this chapter, the committee identifies key, overarching scientific challenges for the years ahead in completing the research portfolio on particulate matter (PM). Chapter 6 offers the committee's recommendations on strategies to most efficiently manage research on PM and address the key information gaps while meeting the scientific challenges laid out in this chapter.

The committee has identified seven overarching scientific challenges for the years ahead in air pollution research; these challenges need to be met for improving the scientific basis for regulation and public health protection and for cost-efficient control:

- Completing the PM emissions inventory and PM air quality models necessary for NAAQS implementation and for informing health research.
- Developing a systematic program to assess the toxicity of different components of the PM mixture.
- Enhancing air quality monitoring for research.
- Planning and implementing new studies of the effects of long-term exposure.
- Improving the relevance of toxicological approaches.
- Moving beyond PM to a multipollutant approach.
- Integrating disciplines.

The regulatory, public health, and scientific contexts are set by the comparatively low concentrations of PM now measured in most of the United States. At these concentrations, the effects found in observational studies are small in comparison to those found in the past, particularly effects observed during dramatic air pollution episodes, such as the 1952 London Fog. The current risks are also small in comparison with those associated with some causes of the same outcomes, for example, active smoking and risk for ischemic heart disease events. Consequently, epidemiologists face the challenge of detecting a relatively weak signal of effect and of ensuring that the effects found do not reflect factors other than air pollution, for example, meteorological conditions and personal use of tobacco products.

The pollutant concentrations of interest also have implications for the design of toxicological experiments and interpretation of their findings. Although it is feasible for epidemiologists to investigate large populations to detect effects, toxicologists typically use exposure levels that are far higher than those experienced by the population to detect measurable effects. Exposures far higher than those experienced by the population generally might be needed to induce measurable effects. Consequently, there might be uncertainty as to the relevance of biological findings in model systems. Mechanisms operative at high concentrations might not be applicable at lower concentrations.

Completing the Particulate Matter Emissions Inventory and Particulate Matter Air Quality Models Necessary for NAAQS Implementation and Informing Health Research

Although the committee recognizes that its objective is to provide independent guidance for planning and monitoring a long-term PM research program, the committee has long acknowledged that this research program should also provide the tools necessary for the implementation of current and possible future PM NAAQSs. In particular, the committee views improved emissions characterization and air-quality model testing and development as critical for rapidly-approaching deadlines for state implementation plans (SIPs). As shown in Table 2-1 of Chapter 2, the states will be developing and submitting their implementation plans over the next 5 years. The committee's second and third reports offered an agenda for research related to these topics. As described in more detail below, EPA should develop a comprehensive prioritized plan for systematically translat-

ing new source-test methods and activity data into a completed, comprehensive national emissions inventory. In addition, source-based air quality models earmarked for regulatory application will be operationally useful only to the extent that the data needed to support them are routinely available. Although EPA alone might not have adequate resources to fully evaluate these models, it can help to shape efforts involving other entities with substantial field monitoring programs to enhance the value of the resulting data for model evaluation. Although some positive steps have been taken by EPA toward further developing the emissions inventories and models needed for the SIPs, the committee sees a need for faster progress in meeting the critical scientific and technical challenges identified in this report. These inventories and models are needed not only for implementation but for subsequent development of control approaches that target those sources of particles linked to the greatest risk to health.

Emission inventories are not only critical for air quality management but also for health research that is directed toward sources rather than toward PM generally. The broad base of need for a complete PM source inventory is not sufficiently appreciated in the committee's judgment. Previous committee reports identified the need for more comprehensive measurements of particle-size distributions, chemical composition, and precursor gases from major stationary, area, mobile, and natural sources. The committee still considers these measurements to be needed in the near term. The measures need to be made with representation of ambient atmospheric conditions and of sources beyond on-road vehicles that contribute major fractions of ambient PM. Methods also need to be developed and applied to better quantify PM and precursor emission rates from in-use engines operating in nonroad environments. The committee is concerned that the challenge of developing methods for this purpose and making the measurements is neither sufficiently acknowledged nor addressed. There are two components to the development of emissions inventories. The first is emission-source characterization, which requires accurate measurements of the mass emission rates, composition, and size distribution from a representative sample of a particular source type. Because of the importance of secondary formation of PM, emission-source characterization also requires emission rates of reactive precursor gases (SO_2, NO_x, ammonia, and volatile and semivolatile organic compounds). To develop a robust and informative source characterization, accurate testing is needed for a sufficient number of units of a particular source category under the full range of possible operating conditions. The second component of emissions inventory development involves applying source-testing information (mass emission

rates, particle-size distributions, and chemical compositions) to estimates of the number of individual units and their use patterns to produce the emissions inventory (see Box 3-1 in Chapter 3). Research is also needed to gather information relevant to this second component.

To control ambient PM concentrations through emissions reductions, the relationship between emissions and ambient concentrations needs to be characterized. An adequate characterization of this relationship is complicated by geographic variability in the natural emissions that contribute to background PM concentrations and in meteorological processes that affect atmospheric processes and also patterns of human exposures. In its second report, the committee addressed the need for research on these topics, with the anticipation that EPA could use monitoring data collected under the PM monitoring programs to greatly improve characterization of the relationships between emissions and ambient PM concentrations. The committee has previously commented that the three activities of emissions tracking, air quality modeling, and ambient monitoring are parallel, complementary and reinforcing. (See topic 4 in Chapter 3 and Appendix C for a discussion of needed improvements in air quality models.)

DEVELOPING A SYSTEMATIC PROGRAM TO ASSESS THE TOXICITY OF DIFFERENT COMPONENTS OF THE PARTICULATE MATTER MIXTURE

To answer the key questions concerning the hazardous components of PM (topic 5), a carefully coordinated, long-term multidisciplinary research effort will be required that goes well beyond the work now under way. Although substantial relevant research has been carried out on this topic, the committee's review showed a collection of evidence with little convergence. The key "lesson learned" is, in fact, the need to reconsider the research strategy for addressing the assessment of hazardous PM components. This topic has proved particularly challenging because of the many aspects of particles that might plausibly determine toxicity and the strong possibility that different characteristics of particles could be relevant to different health outcomes. Additionally, in addressing the topic, coherent and converging evidence is needed from both toxicological and epidemiological research that addresses specific components and health outcomes in parallel.

The barriers to implementing such needed integrated research are scientific, administrative, and perhaps cultural within the research community, and the costs will likely substantially exceed those originally estimated

for the topic of hazardous PM components by the committee. With regard to the scientific approach, models have been lacking for simultaneously pursuing hypotheses in the laboratory and in population contexts. Recently however, several approaches have been taken that might prove to be useful models. For example, the epidemiological studies in the Utah Valley were followed, albeit a decade later, by animal and human toxicological investigation using previously collected particles from the same area (Pope 1989, 1991). As another example, it is possible to use particle concentrators to expose animals for toxicological studies in the same locations where epidemiological studies are in progress. At present, investigators in Southern California are characterizing roadside particles in detail, exposing animals at roadsides in mobile chambers, and carrying out related epidemiological research. A similarly integrated program of research on ultrafine particles has also been implemented.

An additional barrier is the need for population "laboratories" in which hypotheses related to toxicity of PM can be tested. In general, few research groups have either the financial or the technical resources to implement monitoring for assessment of exposure that will be sufficiently detailed to be the foundation for epidemiological research on risks to health and characteristics of PM. As discussed subsequently, the U.S. Environmental Protection Agency (EPA) needs to establish these monitoring sites; the limited success of the agency's coordination of the Supersites Program to provide a sufficient platform for epidemiological research provides an example of the need for coordinated planning involving the health research and monitoring communities to develop sustained multicharacteristic monitoring necessary to inform future population studies. Fortunately, other funding agencies stepped forward and supported research at the Supersites in Fresno, California; Atlanta, Georgia; St. Louis, Missouri; and Baltimore, Maryland. It is also important to gather information about actual exposures of susceptible subpopulations and the general public to particle components of biological relevance.

Finally, the scope of the research task, as described by a matrix with particle characteristics as one dimension and health outcomes as the other, calls for an integrated and more programmatic approach to assessing hazardous PM components. The committee's prior reports addressed the need for integration and interaction in the conduct of its research agenda; the topic of hazardous PM components clearly needs greater integration and interaction than has occurred to date, and the committee strongly recommends that research on this topic should be managed in a more programmatic fashion. Although individual research groups have made advances on specific aspects of particles and health risks, given the heterogeneity of

approaches and the highly selective nature of the hypotheses pursued, the assessment of hazardous PM components will not be addressed with sufficient certainty without taking a new approach.

This new approach is especially important because the research being conducted by different groups is being done without an overarching framework, and the various groups are using different techniques to identify the toxicity of specific components of the PM mixture. Research on hazardous PM components becomes even more challenging when placing the PM mixture in the context of other air pollution components, a scientific challenge identified in more detail below. A plan is needed that approaches the matrix of particle characteristics by health outcomes in an organized and tiered fashion, screening across the matrix with common approaches so that priorities can then be set for a second stage of more focused investigation. Beyond the scientific challenges of developing such an approach, a new management approach will also be necessary (see Chapter 6).

ENHANCING AIR QUALITY MONITORING FOR RESEARCH

Meeting the key research priorities identified in Chapters 3 and 4, especially identification of hazardous components of the PM mixture (topic 5) and the relative role of PM and other copollutants (topic 7), will require an air quality monitoring network designed with sufficient spatial, temporal, physical, and chemical detail to test atmospheric models and to best approximate population exposure rather than solely assessing compliance with the NAAQS. Progress in using epidemiological approaches to understand the toxicity associated with physical and chemical characteristics of PM will depend on the availability of modeling and monitoring data. Such data will be useful in examining relationships among personal exposures to particle components of biological relevance and corresponding ambient concentrations for susceptible subpopulations and the general public.

Monitoring programs in place will provide data that should support exploration of some hypotheses. However, as noted in previous committee reports, these programs are often designed with little input from health and atmospheric scientists, and the programs often do not measure all the PM characteristics of interest and the gaseous pollutants. The gaseous pollutants contribute to the overall burden of pollution-associated morbidity and mortality, and data on their concentrations may be useful for health studies as well as for testing models. Moreover, the frequency of available measurements can be inadequate and weaken some analyses.

Some progress has been made in addressing these challenges, as EPA has implemented the new PM monitoring network. Most notably, the advent of the new PM speciation network, with every-3-day speciation at more than 50 locations, offers opportunities for new research approaches. Limitations can be identified in these initiatives, however; the most notable of which is the slow pace of implementing daily speciation monitoring at the 10 planned sites (at this writing, none of the sites is fully operational, and only five sites have even begun feasibility testing with collocated continuous sulfate, nitrate, and carbon measurements). Another limitation is the slow pace of developing and implementing monitoring programs for ultrafine particles and measurements of soluble metals and organic species. As some recent epidemiological studies suggest, short-term peak exposures (on the order of a few hours) over time and at different locations might be more highly associated with health responses than measures of average pollution concentrations. Thus, continuous measurements might be needed in some locations.

In looking forward, the monitoring paradigm needs to shift increasingly from assessment of compliance with national standards toward serving multiple purposes, such as air quality forecasting, episode alerts, exposure characterization in populations at high risk, health studies, atmospheric process studies, evaluation of source zones of influence, and evaluation of long-term effectiveness of control strategies. This shift implies less use of federal reference methods (FRMs) at urban locations and greater use of in situ continuous monitors and compound-specific integrated samples at locations representing background, boundary, transport corridor, regional, urban, and neighborhood spatial distributions.

Such an enhanced network should have the following characteristics:

- *Use continuous measures of appropriate indicators with real time access.* These measures could be used by local air quality authorities to issue advice and alerts to the public and support the application and improvement of forecasting methods that would permit better public health planning. Public access to these data would permit people to make informed decisions about activities that might affect their personal health. They would allow more precise relationships to be established between the timing of increased concentrations and specific health outcomes. These data would permit better relationships to be established between ambient concentrations and source contributions, thereby better focusing emission-reduction strategies.
- *Represent less uniform micro- and middle-scale exposures.* Many people are exposed to vehicle exhaust near heavily traveled roadways

for at least a portion of the day, and some potential health indicators (for example, black carbon and particle number count) are much lower when measured at a few tens of meters from roadways, as required by compliance siting criteria. A dearth of regional-scale measurement locations also limits the ability to determine the effect of transport from other areas on many air quality planning regions.

- *Encourage the completion of development of continuous monitors for indicators other than mass concentrations.* Much progress has been made in developing continuous instruments for specific chemical components and size distribution at the research level rather than the applications level. A sufficient number of locations requiring these measurements are needed to support an economical instrument production volume and to determine their utility and applicability.

A carefully designed network serving multiple purposes could be implemented by broadening the design of the compliance monitoring work to meet the needs of regulation and research alike. In fact, for both purposes, the nation's monitoring network should be useful for estimating population exposures. It would stimulate new methods for relating ambient concentrations to health outcomes, better estimate human exposure, refine the understanding of particles in the atmosphere, and allow people to make their own decisions about where and when they will perform certain activities that might adversely affect their health.

Several aspects of a new national monitoring strategy are being developed by the EPA's Office of Air Quality Planning and Standards through its proposed national monitoring strategy (known as NCore). This effort is focused on a broad range of pollutants and not only PM and has the potential to move the monitoring system toward a multipollutant approach. However, to date, development of this strategy has involved primarily federal, state, and local air pollution agencies. A need still exists for a broader involvement of air quality and health researchers to optimize national networks for the purposes specified above within the existing resource constraints.

INVESTIGATING THE HEALTH EFFECTS OF LONG-TERM EXPOSURE TO AIR POLLUTION

Epidemiological Approaches

The striking findings of the Harvard Six Cities Study (Dockery et al. 1993), which linked chronic exposure to increased mortality, provided a

strong impetus for reevaluating the PM NAAQS, particularly after their confirmation in the 1995 publication based in the American Cancer Society's Cancer Prevention Study 2 (CPS 2) (Pope et al. 1995). The findings on increased mortality associated with longer-term exposures to higher concentrations of particles suggested that the associations observed in the time-series studies did not reflect only a slight advancement of the timing of death for frail individuals. The findings of the two studies were confirmed with an extensive reanalysis (Krewski et al. 2000) and on further follow-up of the CPS 2 cohort (Pope et al. 2002). Findings from several other cohort studies have also been reported (Abbey et al.1999; Lipfert et al, 2000; Hoek et al. 2002). Although these cohorts have provided critical evidence for long-term effects, evidence from further follow-up of these two U.S. cohorts alone will have little use for decisionmaking. The cohorts were established decades ago, and some critical data items, including residence history and potential confounding and modifying factors, have not been comprehensively updated. Consequently, an increasing degree of exposure misclassification can be anticipated as the participants move from their original residences. And, most important, characterization of current air quality cannot recreate the complex air environments in which the individuals and populations lived and worked in the many years for which data are not available. Long-term studies are likely to remain central, however, in assessing the public health burden caused by air pollution. For quantitative risk assessment and cost-benefit analysis, estimates of the disease burden associated with exposure to particles are needed. These estimates could come from a new generation of studies with more complete information on short- and long-term exposures to PM, its components, and exposures to other pollutants.

Recognizing both the limitations of these studies and the need for ongoing information on long-term exposure to air pollution and health, the committee recommends that research approaches continue to be developed on the basis of existing and new cohorts. Mechanisms are needed for enrollment and tracking of cohorts over time to provide an ongoing characterization of any impact on health of long-term exposure to air pollution. Without substantial commitment of personnel and funds, studies, such as the Six Cities Study and the CPS 2 cohorts, cannot be readily and feasibly undertaken. Rather, such studies might be based on cohorts routinely enrolled for other purposes, for example, investigating cardiovascular diseases (Atherosclerosis Risk in Communities [ARIC 2004] and the Cardiovascular Health Study [CHS 2003]), Medicare participants, and cohorts assembled by the National Center for Health Statistics. However, even such studies will require substantial funding, and their value must be

compared with data collection specifically designed as long-term studies of health effects of air pollution. Medicare has a large cohort under follow-up that is maintained with replacement sampling. The Veterans' Administration also has a large cohort under follow-up. In addition, there might be other opportunities for adding a component related to air pollution and health; the anticipated National Children's Study (2004) is one example. That study might provide insights into air pollution and childhood asthma or lung development, for example. New cohort studies of persons having informative patterns of exposure or heightened susceptibility may also be warranted.

Studies of effects of long-term exposure to PM, based on residence location and other information, need to include large numbers of participants and to incorporate exposure estimates. With information on residence location, the EPA's monitoring data, captured in the Air Quality System (AQS) database (EPA 2004), could be used to estimate exposures. However, these data might not be optimal for health studies, and additional data collection or model data would be needed to better capture population exposure (see Chapter 6). For example, the spatial detail within communities might be better captured with focused monitoring and use of population exposure models. As the AQS data are increased from the new speciation sites and other data-collection efforts, it should become possible to develop estimates for exposures beyond particle mass alone. It is critically important that future monitoring strategies go beyond currently regulated pollutants to allow the testing of a broader range of epidemiological hypotheses.

An additional concern in any cohort study is the availability of information on potential confounding and modifying factors. Life styles and the associated frequency of chronic diseases, particularly heart and lung diseases, are variable across the country. There is a potential for a varying profile of susceptibility to PM across the country and for confounding as well. Some approaches based on population-level data can be identified that might be used to characterize potential confounding and modifying factors. Population-level data are available on tobacco sales, although they are a poor surrogate for actual smoking rates within the cohorts; available data on prevalence of tobacco use and mortality provide an index of the underlying rates of chronic heart and lung disease, particularly coronary heart disease and chronic obstructive pulmonary disease. Population sampling might be done to augment those data resources. However, such population-level data are inherently imperfect measures of individual-level exposures. Some health-system-based cohorts, such as Medicare, include information on diagnoses leading to outpatient visits and hospitalizations. Those data could be used to identify susceptible groups.

The development of new approaches to carrying out these cohort studies will be challenging and time-consuming and should be supported by EPA or other agencies. In 2001 and again in 2003, EPA sought new cohorts for studies of long-term effects through its Science to Achieve Results (STAR) grant mechanism, but it should also support an ongoing planning effort. Although a request has been initiated by EPA to establish a long term cohort to follow up cardiovascular events, it is important for EPA to recognize the need for continued and substantial financial support necessary for these types of studies. At the same time, it will be important for EPA to continue to support additional alternative approaches. The spectrum of human heath effects has expanded over the past several years (see Table 5-1). Because each of these effects has the potential to result in substantial economic and social consequences, as well as significant health impairment, it is important that continued work be undertaken to quantify as much as possible the degree to which PM contributes to these conditions.

Toxicological Approaches

Toxicological approaches have proved to be especially challenging to use in addressing the research topic of assessing hazardous PM components. Further exploration is needed of the role that chronic exposure studies of animals (those encompassing most or all of their life span) can play in predicting human health effects from long-term exposure to PM or enhancing understanding of the mechanisms and exposure-response relationships of the effects. The technology exists to expose rodents (or other species) chronically by repeated inhalation to PM or complex atmospheres containing PM for periods up to the full life span. Many such studies have been conducted in the past, but most were high-dose carcinogenicity bioassays based on study designs that might not be useful for predicting long-term health hazards from current concentrations of PM. Practical considerations limit study group sizes to a few hundred animals in chronic exposure studies, resulting in much smaller cohorts than considered adequate for epidemiological studies. In general, the outcome measures of such studies (life-span shortening and histological, hematological, serum chemistry, body and organ weight, respiratory function, and bronchoalveolar lavage assays) have not demonstrated effects at PM exposure concentrations even well above environmental concentrations. For example, the largest bioassay of inhaled diesel emissions involved exposure of only 220 rats and 360 mice per group and did not demonstrate life-span shortening, cancer, or significant noncancer effects from near lifetime exposures to PM emissions

TABLE 5-1 Putative Health Outcomes Related to Particulate Matter Exposure

Respiratory Conditions	Cardiovascular Conditions	Neuro-behavioral Conditions	Biomarker and Hematological Changes	Growth and Development
Asthma incidence	Arrythmias	Reduced performance	C-reactive protein	Low birth weight
Asthma exacerbations	CVD hospitalizations	Neuro-psychological syndromes	ICAM-8	Increased risk of premature lung development
COPD hospitalization	CVD mortality		Fibrinogen and other clotting factors	Sudden infant death syndrome
COPD mortality	HRV decrease		White-blood-cell increases	
Lung cancer	Blood pressure responsiveness			
Pulmonary function change				
Acute and chronic symptoms				

Abbreviations: CVD, cardiovascular disease; ICAM-8, intercellular adhesion molecule-8; COPD, chronic obstructive pulmonary disease; HRV, heart rate variability.

diluted to 350 micrograms per cubic meter ($\mu g/m^3$) (Henderson et al. 1988; Mauderly 1999). There is little experience in using chronic exposure animal studies to predict noncarcinogenic risks to human health from chronic PM exposure.

Chronic exposure animal studies could prove useful for examining mechanisms and exposure-dose-response relationships for specific health outcomes that are already considered with confidence to result from long-term human exposures. However, making a considerable investment in such a study would require high confidence that the animal model ade-

quately simulated the pathogenesis and expression of the human health outcome of concern and that group sizes were sufficient to detect low-incidence effects that might be relevant in a public health context. The higher the level of confidence that a susceptible subpopulation was being adequately represented by a responsive animal model, the smaller the group size that might be acceptable. Given these conditions, the most contemporary, detailed, and sensitive biological measurements could be incorporated into a chronic exposure study. Until uncertainties about the specific outcomes of long-term human exposures and the fidelity of animal models for human responses to PM are reduced and until hypotheses about the pathogenesis of chronic PM effects are refined, it might not be appropriate to launch long-term animal studies.

A more likely application of toxicological research to understanding the consequences of long-term human exposures to PM lies in the use of studies incorporating repeated exposures ranging from several days to a few months in length to improve the understanding of the mechanisms of effects of such exposures. For example, hypotheses about the effects of chronic PM inhalation on interference with cellular repair mechanisms, antioxidant protection, or immune function might be addressed by intermediate-term, repeated exposures of animals (or, to a limited extent, even by carefully designed clinical studies). Such studies could provide a needed progression beyond evaluation of acute high-dose phenomena to determining the cumulative effects, amplification of effects, progression of effects, or adaptations associated with repeated exposures. Intermediate-term studies could help determine the need for the most appropriate design of future long-term studies.

IMPROVED TOXICOLOGICAL APPROACHES

The committee recognized the need for complementary epidemiological and toxicological evidence in relation to several of the topics, particularly assessing hazardous PM components, combined effects of PM and gaseous pollutants, and susceptible subpopulations. Toxicological approaches have been limited by the difficulty of replicating real-world inhalation exposures to PM in terms of chemistry, by the frequent use of relatively high doses and instillation rather than inhalation of particles in animal studies, and by the inability to readily replicate the human diseases associated with increased susceptibility in animal models. Toxicological

approaches have also proved especially challenging to use in addressing the research topic of assessing hazardous PM components (topic 5). Separating the potential effects of particle size from those of particle chemistry is difficult, because particles of different size can have different chemical characteristics and different rates or routes of clearance, which affect response. Studies of appropriate design are needed, as are well-characterized particle samples for experimental exposures.

Other aspects of the design of toxicological studies will also be relevant in studies directed at assessing hazardous PM components and combined effects of PM and gaseous pollutants. To the extent possible, toxicological studies should include exposures at concentrations that are similar to those in the ambient air. If impossible, then exposure- or dose-response relationships need to be characterized down to concentrations that come as close as possible to ambient concentrations. Achieving that level of comparability will provide some assurance that mechanisms of injury in the toxicological studies are likely to be the same as those operating under the usual conditions of human exposure. Such assurance would allow for more confident extrapolation of toxicological findings relevant to the topics of assessing hazardous PM components and the combined effects of PM and gaseous pollutants. In addition, particles should be delivered in a physiologically relevant manner, that is, by inhalation. Alternative modes, such as instillation, do not result in deposition and clearance processes that fully mimic those occurring in inhalation exposure. Intratracheal instillation and other nonphysiological dosing methods have their place for certain exploratory and comparative purposes, but results need to be validated by inhalation to be considered conclusive.

The committee commented in previous reports on the need for biologically relevant animal models for the chronic heart and lung diseases considered to increase susceptibility to PM in humans. Various models have been developed, attempting to mimic asthma, chronic lung disease, ischemic heart disease, and hypertension. These models can be very useful for exploring specific health hazards and defining specific steps in the pathogenetic chain, but typically fall short of reproducing the full set of exposure-dose-response relationships, susceptibility factors, co-exposure factors, and disease expressions occurring in humans expressing disease after repeated exposure. Categories of potential mechanisms include the following:

- Autonomic nervous system responses.
- Physiological responses.

- Immunological responses.
- Irritant and inflammatory responses.
- Growth and development.
- Cellular responses.

Research on the mechanisms of air pollution effects is proceeding simultaneously with the advancement of cellular-molecular research tools and the understanding of underlying biological mechanisms. For example, gene micro-array techniques are being used in studies of air pollutants even though determination of the most important genes, the roles of the genes, and the best way to evaluate the huge amount of resulting data is still being resolved (see Leikauf et al. 2001). Similar situations exist for interpreting changes in protein products of gene activation, cellular receptor signaling, and the metabolic products of PM-associated compounds and the biological cascades they stimulate. Such studies often have great spin-off benefit by using inhaled toxicants as tools to advance the understanding of biological processes; however, such studies are also often fraught with difficulties in interpreting the results and in determining whether observed responses should be considered adverse. It is appropriate that investigators use the best tools at their disposal to understand the mechanisms of adverse effects from PM and variations in susceptibility and that exposures to pollutant species be used as perturbing agents to study biological response mechanisms. However, until the correspondence between cellular and molecular phenomena and health effects of PM and other air pollutants is well-understood, caution should be used in interpreting cellular and molecular changes as representing adverse effects of PM.

FROM A PARTICULATE MATTER RESEARCH PROGRAM TO A MULTIPOLLUTANT RESEARCH PROGRAM

One further challenge to completing the committee's research agenda lies in the scientifically artificial separation of research on PM from research on air pollution generally. This separation follows the regulatory approach of setting ambient standards for the six criteria pollutants and emission standards without adequate recognition of their interrelationships in the atmosphere and in determining risk to health. Given the need to develop the evidence base for a particular NAAQS, research has too often been driven on a schedule reflecting the cycle of NAAQS review and a

scope restricted to single pollutants rather than air pollution mixtures.[1] The committee's topic 7 identified the need to consider other pollutants along with PM, but more as copollutants than as part of a complex mixture, reflecting the possibly artificial assumption that the criteria pollutants act independently to cause adverse health effects.

The focus on individual pollutants does not square with the underlying science. Atmospheric scientists are always mindful of the dynamic nature of the atmosphere, the myriad chemical reactions taking place, and the variable partitioning of substances between gas and particulate phases. Scientists monitoring the ambient environment or monitoring personal exposures must select sampling methods that provide the best possible characterization of the ever-changing atmosphere. The complex nature of the atmosphere and the potential role of multiple pollutants, and perhaps their combinations, in increasing the occurrence of any given health outcome requires that the investigator also consider the potential roles of pollutants other than the specific pollutant that is the target of current regulatory scrutiny.

Laboratory scientists also need to consider the complexity of real-world emission sources and exposures, even when taking a reductionist approach to studying a specific pathway for a particular pollutant related to a given disease. That is obvious when it is recognized that all humans live in and breathe complex, varying atmospheres of particles and gases arising from multiple sources as primary emissions and from secondary transforma-

[1]In this section, several different terms are used in discussing linkages between atmospheric constituents and human health. The term single air pollutants refers to individual criteria pollutants, such as PM, ozone, or other individual chemical constituents. As will be discussed, much of the past air pollution research has focused on single pollutants. The term multiple pollutants refers to multiple gaseous and PM constituents within a total atmosphere. The term is used fully recognizing that the ambient atmosphere is dynamic in both its spatial and temporal dimensions. The committee advocates at the conclusion of this section that EPA's PM program over time evolve to a multiple pollutant program that includes the traditional pollutants currently classified for regulatory purposes as criteria pollutants, and hazardous air pollutants (including air toxics) and nonclassified atmospheric constituents. The term one atmosphere has been increasingly used in air quality management discussions to refer to an approach that considers in an integrated manner all the atmospheric constituents when air quality management decisions are made on any single pollutant. Because the term "one atmosphere" has not achieved a widely accepted definition, we use the term "multiple pollutant program" in this report.

tions occurring in the atmosphere. The subdivision into criteria pollutants (PM, ozone, oxides of nitrogen, sulfur dioxide, carbon monoxide, and lead), hazardous air pollutants (such as 1,3-butadiene, benzene, and coke oven emissions) and other unclassified chemicals is a reflection of the legislative history rather than a logical scientific taxonomy. Although some pollutants, such as lead, produce specific health effects, the health effects that are associated with most air pollutants typically represent increases in the incidence of chronic diseases that are of common occurrence and have multiple etiologies, such as cardiovascular and respiratory disorders and cancers of multiple organs, or represent exacerbations of these diseases. Moreover, as the concentrations of regulated pollutants in the ambient air continue to fall, even approaching natural background concentrations, the likelihood that specific health outcomes can be ascribed solely or primarily to single pollutants or pollutant classes is likely to be diminished. In addition, among the thousands of compounds in the air, some of them cannot be easily categorized. For example, semivolatiles can exist in either gaseous or particulate form.

In contrast to this broader more inclusive view of multiple pollutants, the current expanded PM research program is an extension of the EPA research program on criteria air pollutants that has been operative for many years. EPA's research on criteria pollutants has been carried out primarily through EPA's intramural laboratories with a much smaller extramural effort carried out under STAR grants, contracts, and cooperative agreements. To a substantial extent, the research program has been loosely linked to the schedule for revising criteria documents and review of NAAQS. Typically, a few years in advance of the development of a criteria document, the level of research on the criteria pollutant under consideration would be increased to fill perceived critical data gaps. As the deadline for inclusion of new published material in the criteria document approached, the level of research on the criteria pollutant under consideration was reduced, and effort was redirected toward the next criteria pollutant to be reviewed. This pattern was typically maintained for all six of the criteria pollutants.

For PM, the epidemiological findings of associations between several PM indicators, especially $PM_{2.5}$, and risks to health resulted in an increase in EPA funding of PM research. The intensity of the debate over the $PM_{2.5}$ NAAQS led Congress to appropriate a further increase in funding for PM research and to direct EPA to contract with the National Research Council to form this committee. The resulting research program is novel in multiple

ways: (1) its strong strategic orientation, (2) its multidisciplinary character, (3) the breadth of the research activities (within the research paradigm outlined by the committee), (4) the involvement of agency laboratories and extramural institutions, including creation of five extramural academic PM research centers and eight PM monitoring Supersites, and (5) level of funding, (6) continuation of a sustained research effort for more than 5 years, and (7) progress made in reducing some of the uncertainties concerning the health effects of PM within certain aspects of the overall research agenda. While attention was focused on PM, the level of research funding for other criteria pollutants was reduced.

Although the PM program has begun to consider other pollutants, it has of necessity focused on PM. Some other air contaminants, largely other criteria pollutants, have been considered in the role of copollutants for their potential impact on the effects of PM. Epidemiologists have largely considered copollutants by determining the extent to which their addition to multipollutant models for data analysis diminished the statistical strength of the association between PM and health outcomes. Even this approach is necessarily limited by the lack of widespread availability of data on environmental concentrations of air contaminants other than the few criteria pollutants whose measurements are mandated for compliance purposes. A few laboratory studies of factorial design have evaluated the effects of PM with and without another pollutant (such as ozone), but factorial designs are not suited for more than three pollutants and thus fall far short of the complexity of environmental exposures; moreover, as stressed earlier, PM itself varies widely in composition. Some studies involving exposures to concentrated ambient PM have also included gaseous pollutants but generally at their original ambient concentration, but the concentration of gaseous agents can be increased if desired. A few laboratory studies of animals and humans exposed to engine emissions have included groups exposed to filtered emissions, thus showing the relative effects of the PM and non-PM fractions.

There is an opportunity and a critical need to shift the focus of the EPA program from a single pollutant, PM, to a multipollutant orientation. Because of the momentum that the PM research program has generated over the past 6 years, now is an opportune time to begin orienting EPA's air quality research program toward a broader scope that specifically considers all components of the atmosphere—PM and the other criteria pollutants, hazardous pollutants, and the other nonclassified components of the atmosphere. The committee envisions a transformation from a PM-focused research program to a multiple air pollutant program (MAPP).

The committee's MAPP concept recognizes that multiple sources contribute multiple pollutants (particles and gases) that are subject to atmospheric transport and transformation. This mixture of pollutants, which varies in composition by time and location, serves as the source of exposures to human populations and ecosystems, resulting in a wide range of adverse effects in humans and ecosystems. The adverse effects that result from the mixtures of multiple pollutants may be attributed to single pollutants or, to a variable and largely unknown degree, combinations of pollutants that together make up an infinitely variable atmosphere. In part, the scientific emphasis on isolating effects of single pollutants follows from the artificial regulatory separation of individual components of the pollution mixture.

The committee envisions the MAPP concept to incorporate as a guiding principle the paradigm advocated by this committee for research on PM (see Figure 1-1 in Chapter 1): source → ambient atmosphere → personal exposure → tissue dose → health response. The committee urges that single air pollutants be considered and addressed in the comprehensive context of the range of multiple pollutant ambient air environments that people actually experience. The committee recognizes that shifting to the MAPP concept will require the development of new scientific approaches to evaluate the linkage of multiple sources of pollutants and multiple pollutants to health effects. This broadened approach should lead to epidemiological study designs and analytical methods that better address the health risks of the components of mixtures and to enhanced toxicological study designs that elucidate biological mechanisms. The improved scientific understanding of the role of pollutants as components of a complex mixture will provide the science base essential for informing future regulatory actions and related control strategies.

The move from a pollutant-by-pollutant orientation to a multiple pollutant orientation is viewed as an evolutionary rather than revolutionary change. Indeed, the multiple pollutant orientation was key to past advances in the scientific understanding of the linkages between primary emissions of PM, volatile organics, sulfur oxide, and nitrogen oxides; atmospheric transformation to ozone and secondary particulates, including sulfates and nitrates; and personal exposure to these mixtures with associated health effects. An understanding of these linkages undergirds the one-atmosphere principle that is emerging to guide air quality management strategies (NRC 2003).

A logical next step in evolving to a MAPP is to develop and implement an integrated research program that includes PM and the other criteria

pollutants, hazardous air pollutants, and currently nonclassified atmospheric constituents. The successes as well as the lessons learned from creating and implementing the PM program over the past 6 years provide building blocks for the broader initiative. Substantial expertise has been mobilized in the intramural laboratories of EPA and in research laboratories of universities and other institutions across the United States. A continually improving science base for PM and other atmospheric constituents is essential for ensuring continued progress in improving total air quality and reducing air-pollution-related health impacts.

Some continued movement toward a multipollutant approach will undoubtedly result from research on hazardous PM components and on combined effects of PM and gaseous pollutants. However, there is a clear need to apply the strategic multidisciplinary orientation that has proved useful for conducting research on PM to the broader study of other criteria and hazardous pollutants.

Methods and models developed by the future PM research program are likely to be useful for studying multiple pollutants. A science-based multipollutant approach can be useful for the development of information relevant to setting standards and developing air quality management strategies. One very important benefit of this approach is the likelihood that the resulting information will aid the understanding of the relative importance of the various pollutants (and thus sources) and their interactions in causing adverse health effects. The approach should be beneficial in optimizing the cost-effectiveness and the "health-effectiveness" of future air quality management strategies. Indeed, it is conceivable that a multipollutant approach to reviewing scientific uncertainties; developing research strategies; conducting research; and analyzing, interpreting, and reporting research findings will extend to developing more integrated criteria documents. That could lead to integrated development of standards, implementation plans, and control strategies that have a stronger science base than that achieved by past single pollutant approaches.

INTEGRATING ACROSS THE DISCIPLINES

The need for complementary evidence on PM from toxicological, exposure, epidemiological, and atmospheric approaches was recognized early by the committee, which called for interdisciplinary research and proposed the PM centers as one mechanism for fostering collaboration across disciplines. Although there has been greater cross-disciplinary

integration of some PM research topics, to a large extent the coordination of epidemiological, toxicological, exposure, and atmospheric research has received more discussion than implementation to date. Expanding multidisciplinary strategies and programs will be essential for implementing the committee's MAPP approach.

The concept of integration across disciplines is both logical and appealing, but it has been difficult in practice to identify research models appropriate for coordinated research or to implement focused interactions between the fields. Exchanges of information between field and laboratory scientists and between scientists studying people directly and those using nonhuman research models are more frequent now than in the past. This improved communication, occurring both within research centers and at scientific meetings, has provided opportunities for the different fields to work in less isolation than a decade ago and to build greater knowledge of other disciplines' research principles and methods; some researchers have taken good advantage of these opportunities. However, research efforts in which epidemiological and toxicological tools are merged in coordinated, preplanned research strategies to answer specific questions remain infrequent.

There are examples of the "hand-off" of research issues between epidemiology**,** exposure research, and toxicology, although none resulted from preplanned coordination of efforts. Perhaps the best example is the demonstration by laboratory studies that the soluble iron content of ambient PM from Provo, Utah, was related to PM toxicity (Ghio et al. 1999) and that these differences corresponded to differences in population health outcomes measured during the times that the ambient particle compositions in Provo varied (Pope 1996). As a second example, the epidemiological evidence for PM-related cardiovascular morbidity and mortality has caused toxicologists to strive to reproduce presumed associations between exposure and effects and to explore underlying mechanisms, such as alterations in cardiac electrophysiology and blood-clotting factors.

Such examples, although providing useful information, have not been sufficiently common. In investigating the health effects of airborne particles, epidemiology researchers have often treated PM as a single agent. Research on airborne particles has made clear the simplifying nature of that assumption, as the chemical and physical complexity of particles in the atmosphere across places and time has been described. To understand the health risks of the PM mixture and the likely differential toxicity of different components of that mixture outlined in the committee's Research Topic 5, and then to increasingly place that understanding in the MAPP context

and to determine the most efficacious methods for reducing emissions and risk will require an entirely new level of collaboration among the disciplines to integrate actual exposures with effects. This integration has begun with efforts by the atmospheric community, through NARSTO,[2] to reach out to the health community and is also evident in some health research that involves increasingly detailed characterization of the PM mixture to which animal and human subjects are exposed.

However, substantially improved integration of epidemiological and toxicological approaches, incorporating improved metrics of atmospheric and personal exposure, will be required to advance the knowledge of PM health effects. For example, laboratory studies of nonhuman biological systems can be designed to explore the basis of causality and describe dose-response relationships, mechanisms of response and susceptibility, markers of exposure and effect, key PM components, and effects of copollutants at a level of detail and precision not possible in the population. As another example, research on emissions characterization and air quality model testing and development could be better integrated. Thus, even better coordination between receptor modeling, grid-based modeling, and emissions research is needed. The specific question is whether the source profiles used in receptor models are consistent with current inventories or whether they indicate the presence of gaps. If so, another question is whether improvements in the inventories lead to better grid-based model predictions.

To some extent, the challenges of integrating disciplines will always be there—differences in the cultures and terminology of different communities of scientists and, to some extent, institutions that conduct the different types of research are inherent, and difficult to overcome. However, the likelihood of success will greatly be enhanced when atmospheric, exposure, epidemiological, and toxicological research tools can be integrated proactively into combined, interactive research strategies to answer specific questions rather than proceeding in parallel to address similar general issues. There are hopeful signs of such efforts, such as the Fresno Asthmatic Children's Environment Study (FACES 2004), which California, EPA, and others are implementing around the Fresno (California) Supersite, and some of the efforts of the PM centers. Much more extensive efforts are necessary, however, to ensure that the full suite of issues related to the health

[2]NARSTO, formerly known as the North American Research Strategy for Tropospheric Ozone, is a multiple stakeholder body organized in 1994 with financial support from the public and private sectors to sponsor public- and private-sector policy-related research on tropospheric ozone and PM.

effects and sources of the complex mixture of pollutants in urban air are better understood over the long term. At a minimum, these efforts should include

- Active collaborative research design.
- A shift by funding agencies toward giving higher priority to research implemented by truly multidisciplinary teams.
- Adequate research funding for projects to allow the active involvement of a full team, including senior investigators from multiple disciplines, if needed.
- Fellowships or sabbaticals that will enable scientists to spend time with groups outside their disciplines.
- Redoubled efforts of appropriate professional societies to hold joint workshops and meetings and to publish proceedings.

Ultimately these efforts will need to result in fully multidisciplinary review, integration, and synthesis of the science by EPA in the criteria document and staff paper processes.

SUMMARY AND CONCLUSIONS

In 1998, the committee recognized that meeting its research agenda would require a substantial investment as well as the development of new research approaches to address complex scientific questions. In reviewing work carried out since that report, the committee has identified seven scientific challenges that should be a focus of further work to complete the PM research agenda. Of course, there are other challenges, but they are not as critical to moving forward on the full agenda. The next chapter gives the committee's guidance on strategies to meet these challenges.

6

The Way Forward

INTRODUCTION

The expanded particulate matter (PM) research program recommended by the present committee was prompted by a widespread scientific and policy concerns that current PM exposures in the United States can cause adverse public health effects. The PM National Ambient Air Quality Standards (NAAQS) promulgated in 1997 were based on the scientific evidence of public health risks from inhaling particles. At the same time, gaps in the available evidence raised questions concerning the scientific basis for the standards that needed to be addressed to strengthen the base of evidence for future PM NAAQS setting and implementation.

Beginning in 1998, with guidance from this committee, the U.S. Environmental Protection Agency (EPA), other agencies, and the scientific community initiated an expanded national effort to address high-priority research needs for PM by targeting research for key gaps in the scientific evidence. This effort was expected to require over a decade-long investment. The pace and scope of PM research have accelerated, and new research findings are available for policymakers engaged in reviewing the scientific basis for the PM NAAQS. There is increasing multidisciplinary exchange involving epidemiologists, toxicologists, exposure assessors, and atmospheric scientists on how best to integrate the work of the various disciplines. A new national monitoring system has been installed that is beginning to provide data on ambient concentrations of $PM_{2.5}$ across the United States, and the sites will soon provide additional detail on particle characteristics across the country. As shown in previous chapters, the research effort is now starting to yield important dividends while raising new questions for further research. The experience to date has also provided lessons in the effective management of research.

However, important issues need to be addressed to ensure sustained

progress most notably the important scientific challenges identified in Chapter 5: developing a systematic program to assess the toxicity of different components of the PM mixture, planning and implementing new studies of the effects of long-term exposure, improving the relevance of toxicological approaches, enhancing the nation's air quality monitoring system, and ultimately moving beyond PM to a multipollutant approach. A shift towards these objectives will require enhanced, multidisciplinary research, and although progress has been made in improving the management of PM research and the gathering and synthesis of information, significant science management challenges remain to be addressed before the goals of the research plan recommended by the committee can be reached. In this chapter, the committee provides guidance on scientific management issues that it expects to be relevant for successfully addressing key priorities for PM research in the future. These issues need to be addressed if the questions identified for continuing research in the previous chapters are to be answered successfully and in a timely fashion.

Specifically, this chapter addresses

- Enhancing and sustaining research and its management at EPA and across the broader research enterprise.
- Tools needed for enhancing the tracking and synthesis of the science going forward.

SUSTAINED RESEARCH MANAGEMENT

The management of any multidisciplinary, multiyear research program is challenging and requires strategic planning, leadership, commitment of a wide range of expertise, and resources. Such management is often more difficult in large public and private institutions where conflicting and changing priorities, institutional fragmentation, and administrative restrictions limit effective program implementation. Yet, sustained, creative management is essential for producing timely results that will provide answers to the key questions posed.

In its previous reports, the committee, recognized the need for this type of management and called for sustained efforts at EPA and other organizations. Management of the PM research program requires the following elements:

- Broadening the scope of and setting priorities for the full range

of issues to be addressed. (The committee's PM research portfolio was a first step toward this goal.)

- Developing and implementing a plan to deploy resources—funding, intramural and extramural researchers, and multiple scientific disciplines—to address the highest priority issues.
- Providing for aggregation and integrative analysis of results and data.
- Tracking and iteratively reviewing progress.
- Communicating issues, approaches, and progress internally and externally.
- Ensuring that PM research is integrated into a broader perspective that encompasses other pollutants.

Although many agencies and organizations have been and must continue to be involved in planning and implementing PM research, EPA has appropriately applied the largest single body of resources and has played the lead role in coordinating the national research effort. The conduct of research at EPA on PM and other major pollutants is a multifaceted undertaking involving the Office of Research and Development (ORD) (intramural research at EPA and extramural research funded through its competitive programs) and the (OAQPS) Office of Air Quality Planning and Standards (air quality monitoring to characterize attainment of the NAAQS and ambient concentrations). Over the past 6 years, in response to funding from Congress and the reports of this committee, EPA took a number of steps toward implementing a multiyear, multidisciplinary PM research program. At the same time, continuing challenges remain for EPA and for the broader scientific community in accomplishing the kind of sustained, creative management that will be necessary to complete the PM research program outlined in the first two reports. The remainder of this chapter pursues the following objectives:

- Briefly review progress to date at EPA.
- Identify key challenges going forward for EPA.
- Consider the need for broader, multiagency implementation.
- Propose the development of a new scientific committee to provide continuing monitoring and advice.

Progress to Date at EPA

Science management at EPA takes place in the context of a large

agency with multiple scientific and regulatory interests and diverse funding priorities. The National Research Council, in its report *Strengthening Science at the U.S. Environmental Protection Agency* (NRC 2000), identified a series of challenges for improving the quality of EPA science (for example, the frequency of changes in goals, priorities, practices, structure, and funding) and called for broad improvements to those efforts, including enhanced ability to identify the most important science issues, the need for effective leadership at all levels, flexibility and accountability for agency research managers, and improved partnerships with the full range of other research entities.

Against this background, EPA applied and redeployed resources and made some progress in implementing the PM research program. Progress included establishment of a formal management structure for PM research, including a top official of EPA's ORD and a national program director for EPA's PM research program to manage the entire intramural and extramural research program; development and implementation of a multiyear research budget; implementing a dramatically expanded monitoring system, including the first nationwide speciated network at over 50 sites; refocusing of key requests for applications for STAR[1] grants to address the priorities set forth in this committee's portfolio; and integration of intramural and extramural efforts in some key areas, especially addressing the elements of the committee's topic 1 (that is, personal, indoor, and outdoor exposures).

In part as a result of EPA's efforts, the PM research program made progress in several areas described in Chapters 3 and 4. At the same time, the continuing need to address still unanswered questions and the challenge of maintaining momentum in the face of changing leadership and priorities require continued attention to enhance EPA's management of this research undertaking. Specific suggestions to accomplish that are discussed in the next section.

Enhancing EPA Research Management

Although progress has been made in implementing the PM research program at EPA, the challenges of implementing an important air quality and public health program and placing it in the context of other pollutants over the long term call for an even greater level of emphasis on science management at EPA. Specifically, in considering the elements of success-

[1]STAR refers to EPA's Science to Achieve Results Program.

ful management described above, the committee identified several key challenges for EPA:

- *Program Management and Leadership:* In response to the committee's earlier reports, EPA for the first time appointed a top official of ORD and a national program director to plan for and coordinate the implementation of the PM research program, and in the first several years of the program, such actions helped to shape a better integrated approach. However, in the past 2 years, the position of national program director, while continuing, has been filled by several individuals on an acting basis for relatively short terms. Although the individuals involved have brought expertise and commitment to these roles, the frequent change-over will substantially undermine the long-term vision and coordination necessary to ensure the program's success if the change-over continues over the long run. Looking forward, the committee sees the continued critical importance of sustained central management and leadership and urges the identification of longer-term appointments to this key position. The functions to be filled by the research will require the sustained appointment of individuals who can, at a minimum, provide sensitive leadership, maintain communication and coordination among agency personnel and investigators in a progressive research agenda, serve as a focal point for communication across the government and outside the government, and redirect the research agenda as needed.
- *Modern Management Tools:* Sustained leadership from talented managers alone will not be sufficient to ensure that a complex research program, involving people from many disciplines working in multiple laboratories in government, academic, and private institutions, is managed in an efficient and effective manner. The program manager and leader and the participating scientists and support personnel need modern program and project management tools that facilitate management. Modern computer-based systems exist that can link goals, financial resources, human resources, and measures of progress together for tracking progress and making mid-course adjustments. Such an approach is of critical importance to the successful management of multiple projects oriented to achieving interrelated goals. EPA does not appear to have such a computer-based management system. When requests were made by the committee to EPA for information on project goals, allocation of resources, past expenditures, or measures of progress (manuscripts published or presentations given), the agency was always responsive, but the response each time appeared to be generated in an ad hoc fashion. Ideally, if a modern management system

were in place, such information could be generated almost instantaneously because it was already in hand. The value of such a system does not relate to responding to external requests but to facilitating the work of program researchers as they work toward common goals in a loosely affiliated network and team.

- *Administrative Flexibility to Deploy Resources:* Any successful research program must have the ability to pursue a mix of research approaches, with investigator-initiated research to capture the fullest creativity of the scientific community balanced with more structured research strategies in key areas where systematic approaches across diverse laboratories and disciplines will be necessary. Through the STAR program, EPA has done much to improve its efforts to fund investigator-initiated research (NRC 2003) and has targeted the research requests in that program to a number of topics identified in the committee's research portfolio. However, while EPA has moved forward on the investigator-initiated aspects of such a program, it has not balanced those efforts with the kind of fully interactive approach that is likely to be needed to accomplish the reduction of key uncertainties, especially those involving the identification of the toxicity of the different components of the PM mixture (topic 5). The imbalance is in part due to the current preference of EPA to use primarily grant and more cooperative agreement mechanisms in managing their research efforts, mechanisms that limit its ability to manage and coordinate the research more actively and to make mid-course corrections as the program evolves. Although these mechanisms are preferred for a reason—to ensure that federal agencies are not unduly directing, and perhaps stifling, scientific investigation—the complex nature of the tasks ahead for PM researchers suggests that the judicious use of more active research management strategies could be appropriate to complement the investigator-initiated approaches. EPA might do that directly or through other mechanisms.
- *Implementing NAAQS for PM:* As discussed in previous chapters, emissions inventory development and air quality model testing and development are two particularly critical issues for the implementation of current and possible future NAAQS for PM. The committee has identified the need for faster progress in these areas, given the upcoming implementation deadlines for the $PM_{2.5}$ NAAQS. EPA should provide more guidance, leadership, and coordination among the groups carrying out air quality modeling and emissions inventory work, particularly those conducting emissions characterization. Some of the needed emission characterizations will be carried out by the states, industry, and other stakeholders. Therefore, EPA will need to assume a leadership role in the development of

testing methods and source-testing performance, the coordination and compilation of results from other source-testing activities, and the updating of the source chemical composition profiles library. The committee's second report recommended that EPA systematically characterize those sources that contribute 80% of the primary particle emissions nationally. Although EPA personnel indicated to the committee that they have ranked sources by their contribution to primary PM emissions, it is unclear whether they are using such information to set priorities for source testing. EPA will also need to ensure that the information developed through this work is quickly made available to state and local agencies as they prepare their SIPs.

EPA's (2001) SIP attainment-demonstration guidance recognizes the uncertainties inherent in air quality simulation efforts by emphasizing a weight-of-evidence approach for showing that emission-control plans will result in sufficient air quality improvements. The attainment-demonstration guidance also emphasizes the complementary application of both source and receptor models to develop a conceptual model that can help guide the selection of appropriate controls. Despite that flexibility, the committee is concerned that the implementation of emission controls to attain the NAAQS may occur without models that have been properly evaluated and have uncertain validity. The committee previously commented that emissions tracking, air quality modeling, and ambient monitoring activities should be viewed as a set of integrated processes, each component supporting the others. Those activities will need to be given some prominence within EPA's research program to facilitate continuous improvement in each of those areas.

- *A Special Effort to Address the Assessment of Hazardous PM Components:* The need for enhanced science management becomes especially important when one considers the extraordinary scientific challenge posed by the assessment of the hazardous components of the PM mixture. The committee urges EPA to assume strong scientific leadership in relation to this topic. Sustained and intensive management by EPA should be substantially beyond its efforts to date, and it should have an effective mechanism for the active involvement of the full range of public and private sector research organizations. Integrated planning and augmented management structure are needed within the Agency and across the scientific community. These efforts should not be only an expanded version of "business as usual." They will require the active and coordinated management of science in a way reminiscent of other major national scientific initiatives to develop key new technologies or to find cures and treatments

for important diseases. Although this undertaking will be costly and time consuming, the large size of the public health benefits and the potential private sector control costs will make the cost of such a research initiative small by comparison. Implementing such overarching management will benefit science and public policy substantially. But at the same time it must be implemented in a way that both brings together the scientific community in a coordinated fashion, even while ensuring that the individual innovation and creativity that different scientists can bring to the task can still contribute to the results. Maintaining this balance will be essential to the successful conduct of this important undertaking.

To implement such a program, a specific plan is needed that approaches the matrix of particle characteristics by health outcomes in an organized and tiered fashion, screening across the matrix with common approaches so that priorities can then be set for a second stage of more focused investigation. Beyond a plan, mechanisms are needed for the integrated implementation of research in a public and private partnership. An umbrella organization of the involved institutions might be needed to ensure coordination as well as efficiency in assessing hazardous PM components. Outside scientists should be involved from the outset, most likely through a steering or coordinating committee for this topic that draws on both intramural scientists, including health researchers and exposure and monitoring experts, and extramural scientists from the full range of appropriate disciplines and institutions.

- *Developing Future Human Resources:* Accomplishing this objective requires not only talented leadership at the top but also development and renewal of trained investigators prepared to work in the required multidisciplinary arenas to meet the key scientific challenges identified in Chapter 5. Training a new generation of scientists is an essential part of any future sustained effort to explore health effects and atmospheric research in a PM or broader air pollution program. Training will need to be supported and fostered at the doctoral and post-doctoral level and within the research community of the federal government, particularly EPA. EPA had a training fellowship program that has been helpful, but budgetary support for that program has not been stable. Beyond that program, the need for such training and the mechanisms to implement it were described in valuable detail in the NRC report on strengthening science at EPA (NRC 2000).
- *Data Aggregation and Analysis:* One key role for EPA, as a central manager of this program, is to ensure the timely collection, importation into accessible central databases, and analysis of the results and data produced by the PM research program. This role cuts across the entire

program and has been pursued in some cases, such as the multiparty efforts to collect and synthesize data on personal exposure. However, the development of such integrated approaches has been more difficult in other cases, for example, in the Supersites Program. Both the committee in its first reports and others (for example, a workshop on monitoring airborne PM [Albritton and Greenbaum 1998]) recommended that the Supersites Program be designed from the start as an integrated program that could meet the needs of multiple monitoring technology, modeling, exposure assessment, and health. Although the program has produced useful data on a site-by-site basis, and efforts have been made to compile the data in a central database, the program was not designed and implemented in an integrated and systematic manner with analysis plans built in from the beginning. This substantially limits the future usefulness of its results. To date, little funding has been made available for research efforts to analyze the wealth of data across all the sites and cooperating programs.

Beyond these specific challenges, tracking and synthesis of the scientific literature need to be substantially enhanced as the results of this PM program continue to appear (see Improved Tools for Science Tracking and Synthesis below).

Developing a Broader Multiagency Research Program

Research on PM has expanded substantially over the past decade. Support has come from a wide range of government agencies and other research funding organizations. Although EPA has been the single largest investor in such research, and its program has been a focus of the committee's attention, the PM research community includes many other U.S. federal and state government agencies (for example, the U.S. Department of Energy [DOE], the National Institutes of Health [NIH], the National Oceanic and Atmospheric Administration [NOAA], National Science Foundation [NSF], and the California Air Resources Board [CARB]), a number of international funding organizations (for example, the European Union), several nongovernment funding organizations (for example, the Electric Power Research Institute [EPRI] and the Health Effects Institute [HEI]), and industry. Planning and management of research across government agencies and other organizations present a number of continuing challenges, including (1) specific agency missions and differing needs and priorities for research; (2) variability in planning processes and management

systems; (3) differing standards and expectations for ensuring research quality and applying research to policy development; and (4) competition among agencies for resources and influence.

Those and other challenges affect the coordination of PM research across funding agencies, and a lack of sufficient coordination could undermine the effectiveness of research. Coordination has been enhanced through several mechanisms, including (1) EPA as the lead agency in PM research planning can leverage ideas and have some influence on other funding organizations; (2) Congress can participate actively through appropriations, oversight, and staff interest in PM research planning; (3) in part in response to the committee's earlier reports, an interagency mechanism, the PM workgroup of the Air Quality Research Subcommittee of the Committee on Environment and Natural Resources (CENR), was created to exchange information and plans. Other organizations, such as NARSTO,[2] have also provided opportunities for exchange among diverse federal, state, and private organizations, and the online PMRA.org research database developed by EPA and the Health Effects Institute (HEI) has provided a central inventory of the many different activities in the United States and elsewhere.

The CENR PM workgroup and 19 other agencies participate in PM research activities. To date, the workgroup's activities have focused primarily on sharing information about the PM research activities of federal agencies. It has, however, stopped short of the type of integrated planning and implementation called for in the committee's reports.

CENR's efforts have also been limited to federal agencies, leaving the broader communication among diverse programs to NARSTO. NARSTO has recently completed an assessment of atmospheric science relevant to PM that presents recent findings of PM atmospheric science for North America (NARSTO 2003). Beyond CENR and NARSTO, scientific professional societies, industry research organizations, and organizations based on multiple stakeholder partnerships, such as the HEI, are other avenues for research coordination. For the most part, these efforts have provided useful avenues for information exchange, but with a few exceptions (for example, the Fresno Asthmatic Children's Environment Study [FACES] supported by the California Air Resources Board and coordinated with the Fresno Supersite), none of them has gone beyond information sharing and descrip-

[2]NARSTO, formerly known as The North American Research Strategy for Tropospheric Ozone, is a multiple stakeholder body organized in 1994 with financial support from the public and private sectors to sponsor public- and private-sector policy-related research on tropospheric ozone and PM.

tive activities to create proactive cross-agency research planning and implementation. These efforts have been valuable but have not affected decisions on how the individual agencies allocate and spend their funds.

The committee concludes that existing interagency research coordination efforts to date have helped promote greater awareness of PM-related research needs among federal and state agencies, academic scientists, the private sector, segments of the international research community, and nongovernment stakeholder organizations. However, effective coordination among these parties has not yet been achieved.

The committee recommends that the following additional steps be taken to improve interagency research coordination:

- Establish multiagency and agencywide research goals and measures for determining the degree of success in meeting these national goals.
- Prepare a multiyear plan for PM research across agencies that states specific research strategies and priorities for achieving PM research goals, provides a staged transition to integrating those goals into a multipollutant approach, and incorporates state and private activities into the federal program. EPA is now working on a multiyear plan for its PM research program (EPA 2003b).
- Obtain periodic independent scientific reviews of the multiyear plan and related goals, measures, strategies, and priorities.
- Define the specific roles and responsibilities of individual research funding agencies and communicate how their individual plans and capabilities are integrated within a single national multiyear plan, which might ultimately take the form of a unified air pollution research budget across federal agencies.
- Enable other nonfederal PM research funding organizations to provide continuing input into the federal planning process, and seek opportunities for additional PM research partnerships.
- Expand the transparency of the federal PM research planning process to nongovernment stakeholders.

Beyond these national and North American efforts, international cooperation in air pollution research should also be enhanced through expanded bilateral and multilateral agreements. Such an effort could be highly valuable for national regulatory policies by providing early access to findings of research conducted in foreign countries.

Air pollution by PM and the other pollutants is a national and interna-

tional public health issue that should be coordinated by the many involved governmental and other partners, even though EPA is by mandate in the lead on scientific research and regulation. The committee has not seen sufficient proactive integrated research planning and implementation among the many agencies over the past 6 years, integration that is essential for achieving important and difficult research goals, such as understanding the toxicity of different components of the PM mixture, designing and conducting research on the long-term effects of exposure, and testing models appropriate to use for PM control strategies. The steps listed above are essential and, if taken, will lead to more robust and cost-effective PM research planning and can increase public confidence in the results obtained.

Need for an Ongoing Planning and Oversight Committee

The Committee on Research Priorities for Airborne Particulate Matter was established to develop a policy-relevant scientific agenda for research on airborne PM, monitor progress toward achieving this agenda, and evaluate the gains and benefits of the knowledge acquired. The committee developed several useful tools for conducting its work, including (1) a research portfolio to define and track research needs and progress; (2) a framework to synthesize available information and evaluate the extent to which scientific uncertainties were reduced; and (3) criteria to assess the value of research to policymaking, measure the quality of the research, and determine the extent to which the research was effectively planned and made available to the scientific community and other interested parties.

The completion of this committee's task through the issuance of this report does not complete the need for ongoing PM research, nor is the task of independently reviewing PM research plans and results finished. Beyond those tasks, the need to move this research agenda increasingly toward a multipollutant approach for health effects and to better inform implementation strategies poses new challenges and opportunities. These tasks are an inherent part of ensuring policy-relevant and high-quality research that sustains public confidence in the process of setting NAAQS.

The need for sustained oversight and advice on implementing this complex research program has grown since 1998. However, such advice is best not given by the same group that has been so closely tied to the development of the program but by a new body that can sustain the effort and bring forth new ideas and direction. The committee recommends, upon

the issuance of this report and the completion of its task, that both EPA and Congress consider establishing a successor to this committee through the year 2010—the time frame for completing the PM research portfolio. Moreover as emphasized elsewhere in the report, it is important that oversight and advice not focus exclusively on PM but also consider other atmospheric constituents that impact on health. There are several ways in which such an ongoing independent mechanism might be established, but several of the principles followed in establishing the current committee could help guide that process. These principles include the following:

- A committee representing a diversity of scientific skills, experience in research management, knowledge of policy development, and varied institutional affiliations.
- The ability of the committee to engage actively with relevant decisionmakers and participants in the process for managing PM research and setting PM NAAQS so as to assess the most important questions to be answered.
- A focus not only on the near term but also on identifying and evaluating research plans and results relevant to short-, medium- and long-term time horizons in ways that reconcile the needs of both scientists and policymakers.

In establishing a new mechanism for independent guidance, care should be taken to balance continuity and fresh thinking by ensuring that the majority have not been involved in the work of the current committee. This new effort should extend its work beyond EPA to include review of PM-related research; plans and budgets across the federal government; and agencies, public and private, other than the federal government. Indeed, there is considerable merit to chartering this new effort to consider broadly all air pollutants and their relationship to health, recognizing the extent to which the effects of individual pollutants are interrelated with those of others.

IMPROVED TOOLS FOR SCIENCE TRACKING AND SYNTHESIS

In the 6 years since the first report of this committee, substantial new literature has been reported that is relevant to the committee's task. In preparing this report, the committee reviewed hundreds of scientific reports.

EPA's fourth external review draft criteria document on PM (EPA 2003a), which focuses on new reports since the 1996 criteria document, includes more than 3,200 references in its more than 1,800 pages. The committee developed its own database to organize the most critical references, but the full number of relevant studies could not be captured.

The magnitude and scope of this new science, and the even greater volume of research likely to report out in the coming years, pose both an opportunity and challenge. It provides a rich new resource for understanding the sources and effects of PM. At the same time, the scope of the literature available now exceeds the capacity of the usual integrative mechanism of expert review, given the need to summarize substantial literature on any single facet of PM and to synthesize across different lines of investigation. The committee has identified two key ways to address this substantial opportunity and challenge.

Ongoing Inventory of PM Research and Publications

One positive result of the committee's earlier reports, and EPA's implementation of the PM research program, is the development of an interactive, web-based, searchable database of all PM research projects (HEI/EPA 2003). This database contains the projects of all major PM research funding organizations and is searchable by investigator, research focus of project, funding institution, and other variables. It is regularly updated with new projects funded by EPA, HEI, and some other federal agencies, but the process of updating is difficult, especially for atmospheric studies that are funded by multiple agencies. The ability to continue to gain cooperation from other federal agencies is probably also tied directly to the sustained involvement of the EPA program manager.

Perhaps more important, no equivalent effort has been made to develop and maintain a database of all newly published PM research from all relevant fields, including health, exposure, and atmospheric chemistry. Although a catalog of the manuscripts included in the criteria document was developed, that catalog, although machine-readable, is not maintained in a searchable database with key aspects and results of the studies included. The catalog is likely to be kept up to date only until the current criteria document is completed, at which time the process is likely to be suspended until the next PM NAAQS review. The catalog is also not available on the web or in other ways to those in the broader research community who are planning studies and waiting to compare their results with other emerging

data. For both the ongoing review of the NAAQS standards that are required every 5 years, and to support implementation decisions for the NAAQS, EPA will benefit substantially from developing, implementing, and maintaining such a database.

To move forward, EPA should maintain a fully searchable, semiannually updated database of the literature on PM. This database should evolve through stages to include the other air pollutants that make up the atmosphere and should be established and funded in such a way to ensure continued attention to maintaining and updating. Development of this database is not a simple undertaking but is one that should pay dividends to EPA and the broader science community for many years to come. It is also a logical and achievable extension of EPA's current efforts, in which it already invests substantial resources in identifying scientific publications and organizing findings in the form of criteria documents and other reports. Types of models for such efforts include the much larger Medline database or a more modest searchable database using readily available software to identify publications that address specific aspects of PM research, such as PM exposure in older subgroups.

Improving Information Synthesis

In addressing its charge of gauging research progress, the committee needed to develop an approach for synthesizing research findings. This process is set out in Chapter 2. Even though committees of the National Research Council and of other agencies frequently take on the task of evidence synthesis, the committee found few directly applicable models for this task.

Although many NRC committees are charged with judging causality based on evidence, gauging uncertainties, or evaluating agency research programs, the charge for the committee of this report was focused on judging research progress in terms of scientific and policy value. Although causality of the association of an environmental agent with one or more health effects is a key part of the rationale for developing regulatory standards, our goal was to examine the extent to which uncertainty had been reduced in addressing the 10 research topics that we had framed. Research results on these topics were also available from many fields, requiring us to develop means to synthesize findings and assess progress across research results from multiple scientific disciplines. Despite extensive literature searches and discussions with experts about possible strategies, we were

unable to locate a method previously used for such interdisciplinary research synthesis.

As a result, we developed an approach to meet our charge. We gathered and evaluated research from a wide range of fields—from environmental and source monitoring and modeling to statistical methods, epidemiology, exposure assessment**,** toxicology, and clinical studies. We examined the quality of studies, judging them on the basis of the standards for the applicable academic discipline. For each topic, we examined the research from each contributing field and developed an overall judgment of the reduction in uncertainty that had occurred for that topic. We considered the state of understanding in 1997 and the amount of new information gained over the following 5 years. Our assessments of progress and scientific and policy value reflect our collective decisions about research progress for each topic (Appendix C).

The body of scientific evidence on PM and other air pollutants is only likely to grow in scope and complexity, and whether future decisions concern NAAQS or setting priorities for control strategies, they will demand enhanced tools and a protocol for assessing and synthesizing the evidence. Such techniques will benefit all decisionmaking agencies, as well as any successor to this committee (as recommended above) and other advisory committees. A standardized approach will make reviews of research programs more efficient, accessible, and comparable across institutions. More experience with methods such as this committee's is likely to result in continual improvements in strategies for synthesizing and learning from the committee's substantial investment in developing new answers to difficult questions.

CONCLUSION

The progress to date on meeting the committee's research agenda is the result of sustained efforts by EPA, many other organizations, and the scientific community. The continuing needs for scientific research identified in Chapters 4 and 5 will require an even more intensive and well-managed program, both maintaining the momentum that has begun and addressing the underlying management challenges for EPA and other research agencies that have not been addressed to date.

7

Conclusion

The importance of enhancing the understanding of the relationship between airborne particulate matter (PM) and health has led the nation to embark on a multiyear, multidisciplinary research program designed to inform decisions on the PM NAAQS and to evaluate the effectiveness of source control strategies. During its tenure, the committee has had the opportunity to propose a research agenda, monitor its implementation, and gauge initial progress in reducing key scientific uncertainties. This 5-year experience has provided an opportunity to make observations concerning the process of initiating and subsequently managing a large multidisciplinary research program. Through this process, the committee identified some strengths and weaknesses of research and management approaches. The committee has also seen some of the initially recommended studies reach publication and then enter into EPA's process of NAAQS review.

Overall progress to date on several of the committee's priority research topics is encouraging and demonstrates that some of the key uncertainties can be addressed quickly by using targeted research initiatives, as in the example of research on outdoor concentrations versus actual human exposure (topic 1). It is not surprising that much research remains to be done from the committee's original research agenda, as detailed in Chapters 3 and 4. That conclusion is especially true for the related topics of characterization of emission sources (topic 3) and air quality model development and testing (topic 4), which are critical to informing future decisions, as well as assessment of hazardous PM components (topic 5).

Beyond continuing to seek the answers to these specific questions, the committee has identified seven important scientific challenges that need to be addressed as implementation of the committee's research portfolio proceeds:

- Completing the PM emissions inventory and developing and testing air quality models for the implementation of current and possible future PM NAAQS.
- Developing a systematic program to assess the comparative toxicity of different components of the PM mixture and of the mixture itself.
- Planning and implementing new studies on the effects of long-term exposure.
- Improving the relevance of toxicological approaches.
- Enhancing the ability of the air quality monitoring system to track progress and serve as an element for estimating exposure for future health research.
- Moving beyond PM to a multipollutant approach to improve air quality overall in a health-relevant manner.
- Integrating disciplines.

Some progress has been made in addressing these challenges (for example, the implementation of the nationwide speciation monitoring network), but these seven issues need careful attention as the PM research program continues. By addressing these issues directly, it is the committee's judgment that the pace of scientific gain should be quickened, and the quality of research evidence strengthened.

These issues also pose important challenges to the management of science. To be able to address them effectively, Chapter 6 has identified a series of steps that must be taken to effectively manage this complex scientific enterprise, which can be grouped into three broad categories:

1. An even higher level of sustained integration and interaction both among the scientific disciplines and among the full range of public and private research funding organizations will be needed to complete the research portfolio.
2. Much stronger tools will be needed to compile and synthesize the large amounts of new information being developed in this research program.
3. Perhaps most important, sustained and substantially enhanced management of this program by EPA, accompanied by a continuing mechanism for independent review and oversight of the program, will be the only way to ensure that the investment in the research is being made. EPA has taken steps toward better management, but recent transitions in the management of that effort and a substantial need for new management systems and

administrative mechanisms for supporting research, especially on the topic of assessment of hazardous PM components, suggest that EPA will need to enhance its efforts. Equally important will be the development of some form of a successor to this committee to provide continued monitoring and guidance to the efforts of EPA and others.

Much has been learned since 1998 research investment, and the evidence gained by the investment is already being used in the decisions that will continue to be made even with the uncertainties. Much is still to be learned. A failure to invest in advancing the understanding of the effects of PM and air pollution on health risks would result, in general, in not taking full advantage of the substantial research investment to date and limiting the nation's ability to make evidence-based health policy and air quality regulatory choices in the future. Alternatively, continued enhancement of the air pollution and health research effort will undoubtedly yield substantial benefits for years to come. It is clearly the latter choice that offers the most promise to the nation in its effort to improve air quality and public health.

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Terms and Abbreviations

AER: air exchange rate
Aerosol: a suspension of solid and/or liquid particles in a gas
Attenuation factor: fraction of ambient particles to which humans are exposed
Black carbon: a general term often used interchangeably with "elemental carbon" or "soot."
CAA: Clean Air Act
CAPs: concentrated ambient particles
CARB: California Air Resources Board
CASAC: Clean Air Scientific Advisory Committee of the U.S. Environmental Protection Agency (EPA)
CEM: continuous emission monitor
CFR: Code of Federal Regulations
CO: carbon monoxide
COPD: chronic obstructive pulmonary disease
Criteria document: an encyclopedic document prepared by EPA with assistance from the larger scientific community that describes the characteristics and potential human-health and public-welfare effects of criteria pollutants
Criteria pollutants: The Clean Air Act requires EPA to set National Ambient Air Quality Standards (NAAQS) for certain pollutants known to be hazardous to human health and the public welfare (for example, damage to forests and degradation of atmospheric visibility). In addition, these pollutants should be ones whose presence in ambient air results from numerous or diverse mobile or stationary sources. EPA has identified and set standards to protect human health and welfare for six pollutants: ozone, carbon monoxide, particulate matter (PM_{10} and $PM_{2.5}$), sulfur dioxide, lead, and nitrogen oxide. The

term criteria pollutants derives from the requirement that EPA must describe the characteristics and potential health and welfare effects of these pollutants. It is on the basis of such criteria that NAAQS are set or revised.

EC: elemental carbon
EPA: U.S. Environmental Protection Agency
EPRI: Electric Power Research Institute
FRM: federal reference method
FTP: federal test procedure
GAM: generalized additive model
GLM: generalized linear model
GIS: geographic information system
HEI: Health Effects Institute
HRV: heart rate variability
IMPROVE: Interagency Monitoring of Protected Visual Environments
MAPP: Multiple Air Pollutant Program
Microenvironment: A three-dimensional space with a volume in which contaminant concentration is spatially uniform during some specific interval
NAAQS: National Ambient Air Quality Standards
NMHC: nonmethane hydrocarbon
NH_3: ammonia
NMMAPS: National Morbidity, Mortality, and Air Pollution Study
NO_2: nitrogen dioxide
NO_x: oxides of nitrogen (NO and NO_2)
NRC: National Research Council
O_3: oxygen
OC: organic carbon
PM: particulate matter
$PM_{0.1}$: particles less than 0.1 μm in aerodynamic diameter, called ultrafines
$PM_{2.5}$: particles less than 2.5 μm in aerodynamic diameter, called fine particles
PM_{10}: particles less than 10 μm in aerodynamic diameter
$PM_{10\text{-}2.5}$: particles between 2.5 μm and 10 μm in aerodynamic diameter, called coarse particles
PM_{10+}: particles greater than 10 μm in aerodynamic diameter (particles not assumed to be respirable)
ROFA: residual oil fly ash
SAB: EPA's Science Advisory Board

SO_2: sulfur dioxide

Staff paper: Prepared by EPA, the staff paper translates the scientific advances that are described in the criteria document into potential policy options, including possible revisions to the four elements of the NAAQS: pollutant indicator, averaging time, statistical form, and the level.

STAR: Science to Achieve Results

STN: speciation trends network

Time-series study: epidemiological studies that evaluate associations between changes in health effects and changes in exposure indicators (for example, ambient PM concentrations) preceding or simultaneous with the observed outcome

TSP: total suspended particles

VOC: volatile organic compound

Appendix A

Biographical Information on the Committee on Research Priorities for Airborne Particulate Matter

JONATHAN SAMET (*Chair)*, Johns Hopkins University, Baltimore, Maryland

Jonathan Samet is professor and chairman of the Department of Epidemiology at The Johns Hopkins Bloomberg School of Public Health. Dr. Samet earned his M.D. from the University of Rochester School of Medicine and Dentistry and an M.S. in epidemiology from the Harvard School of Public Health. He is board-certified in internal medicine and the subspecialty of pulmonary disease. He was formerly professor and chief of the Pulmonary and Critical Care Division in the Department of Medicine at the University of New Mexico School of Medicine. He is past-president of the Society for Epidemiologic Research and the American College of Epidemiology. He has served on the U.S. Environmental Protection Agency (EPA) Science Advisory Board. He is an editor of the *American Journal of Epidemiology*. Dr. Samet was awarded the Surgeon General's Medallion in 1990. He was elected to the Institute of Medicine in 1997 and currently serves as chairman of the present committee. He also served as chairman of the NRC Committee on Health Risks of Exposure to Radon (BEIR VI). He is also chair of the NRC's Board on Environmental Studies and Toxicology.

JUDITH C. CHOW, Desert Research Institute, Reno, Nevada

Judith Chow is a research professor at the Division of Atmospheric Sciences, Desert Research Institute, University and Community College System of Nevada. She earned her Sc.D. in environmental science from

Harvard University. Dr. has been a major collaborator in more than 50 air quality studies and is currently co-principal investigator on several studies including the evaluation of aerosol measurement methods, sampling strategies, and data bases. She authored the Air & Waste Management Association's 1995 annual critical review on aerosol measurement methods and has over 100 peer-reviewed publications. She serves as air group coordinator of the Air & Waste Management Association and as the chair of the critical review committee under the organization's technical council. She also serves as chair of the Metals 1 Subcommittee of the Intersociety Committee for Methods of Air Sampling and Analysis. She is chair of the editorial review board for the Journal of Air and Waste Management Association and member of the editorial review board of the *Journal of Scientific World*. She is currently a member of NRC's Board on Environmental Studies and Toxicology.

BART E. CROES, California Air Resources Board, Sacramento, California

Bart Croes is the chief of the Research Division at the California Air Resources Board. He received his B.S. in chemical engineering from the California Institute of Technology and his M.S. in chemical engineering from the University of California at Santa Barbara. He was the program manager for the 1997 Southern California Ozone Study and Aerosol Program, and former manager of atmospheric processes, particulate matter, and acid deposition research at the California Air Resources Board. He is on the Executive Steering Committee for NARSTO and he has served on several EPA peer review panels.

ROBERT E. FORSTER, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

Robert Forster is Isaac Ott Professor Emeritus in the Department of Physiology at the University of Pennsylvania School of Medicine. He received his M.D. from the University of Pennsylvania, is a former chairman of the department of physiology at the University of Pennsylvania, past-president of the American Physiological Society, and was awarded a Von Humboldt Prize in 1993. Dr. Forster was elected to the National Academy of Sciences in 1973 and has served as chair of NAS Section 23 (Physiology and Pharmacology) and as a member of several NRC committees. Dr. Forester's interests are in respiratory physiology; in particular on the kinetics of oxygen, carbon monoxide, and carbon dioxide processes in related exchanges.

DANIEL S. GREENBAUM, Health Effects Institute, Boston, Massachusetts

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Roger McClellan is currently a private consultant in inhalation toxicology and human health risk analysis. He is president emeritus of the Chemical Industry Institute of Toxicology (CIIT), having served as president of CIIT from 1988 to 1999. He is a former president and director of the Inhalation Toxicology Research Institute, Lovelace Biomedical and Environmental Research Institute, which now operates as the Lovelace Respiratory Research Institute. Dr. McClellan earned his D.V.M. from Washington State University and is a diplomate of the American Board of Veterinary Toxicology and the American Board of Toxicology. He has served or is serving on the adjunct faculty of the University of New Mexico, Colorado State University, Washington State University, Duke University, North Carolina State University, and University of North Carolina-Chapel Hill. He has served on numerous government advisory committees, including the National Institutes of Health (NIH) toxicology study section, Naitonal Institute of Environmental Health Sciences (NIEHS) advisory council, CDC National Center for Environmental Health, Department of Energy (DOE) Biological and Environmental Research Advisory Committee, EPA's Science Advisory Board and as chair of EPA's Clean Air Scientific Advisory Committee. He is a past president of the Society of Toxicology (SOT), the Inhalation Specialty Section of SOT, and American Association for Aerosol Research and a fellow of the Society for Risk Analysis, the Health Physics Society, and the American Association for Advancement of Science. He serves or has served on various editorial boards including the *Journal of Fundamental and Applied Toxicology*, *Environmental Health Perspectives*, *Journal of Toxicology and Environmental Health,* and *Inhalation Toxicology* and serves as editor of *Critical Reviews in Toxicology*. He has received special awards from the Society of Toxicology, Health Physics Society, American Association for Aerosol Research, the International Society for Aerosols in Medicine, and the International Society of Regulatory Toxicology and Pharmacology. Dr. McClellan was elected to the Institute of Medicine in 1990. He is a former chair of the NRC's Committee on Toxicology and has served on several other NRC and Institute of Medicine committees. He has a long-standing interest in the toxicology and assessment of human risks of airborne materials.

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Appendix B

The Committee's Statement of Task

The committee will assess research priorities, develop a conceptual research plan, and monitor research progress toward improved understanding of the relationships between airborne particulate matter (PM), its various sources, and its effects on public health. The study will focus on PM-related research being conducted, funded, or planned by the U.S. Environmental Protection Agency (EPA) in the context of PM-related research being conducted, funded, or planned by other agencies and organizations in the United States and abroad.

Four reports will be prepared. The first report, required by Congress within four months of project initiation, will be a brief interim report identifying the most important short-term (3 years) research priorities relevant to evaluating, setting, and implementing primary National Ambient Air Quality Standards (NAAQS) for particulate matter (PM). It will be followed by three major reports. The first major report, required by Congress within 12 months of project initiation, will expand upon the assessment of short-term research priorities, identify longer-term research needs, and present conceptual plans for research and the monitoring and evaluation of research. Subsequent reports at the end of the third and fifth years will evaluate research progress and update the research priorities and plans as warranted. The project was started in December 1997 and is sponsored by the EPA.

Appendix C

Detailed Assessment of Particulate Matter Research Progress

In this appendix, the committee reviews progress made in implementing the particulate matter (PM) research portfolio from 1998 (the year in which the portfolio was first recommended by the committee) until the middle of 2002. Some additional updating was done over the next year as this report was written. The focus of the committee's evaluation has been research funded by the U.S. Environmental Protection Agency (EPA) with additional consideration of other funding organizations in the United States and abroad. The committee's evaluative approach is described in Chapter 2. Table 1-3 in Chapter 1 summarizes the levels of funding allocated to the 10 categories of research recommendations by this committee.

For each of the 10 topics in the research portfolio, the committee considers the state of understanding at the end of 1997 and the types of research projects started shortly thereafter. The committee also considers what has been learned since 1997 as well as the scientific value and decisionmaking value of that evidence. In addition, the committee discusses information expected to become available in the near future from ongoing research, major remaining uncertainties, and remaining tasks.

RESEARCH TOPIC 1
OUTDOOR MEASURES VERSUS ACTUAL HUMAN EXPOSURES

What are the quantitative relationships between concentrations of particulate matter and gaseous copollutants measured at stationary outdoor air-monitoring sites, and the contributions of these concentrations to actual

personal exposures, especially for potentially susceptible subpopulations and individuals?

Introduction

Compliance with the National Ambient Air Quality Standards (NAAQS) for particulate matter (PM) is ascertained by measuring ambient concentrations of PM at monitoring sites. With regard to the health effects of air pollution, the risks depend on personal exposure—that is, the exposures received by people in the various specific places, conceptualized as microenvironments, where they spend time. Total personal exposure represents the time-weighted average of particle concentrations in the microenvironments where people spend their time. Exposures to particles generated by outdoor sources take place not only outside but also in indoor environments where the particles penetrate. Indoor particle sources, such as cigarette smoking, thus might contribute substantially to total personal exposure to particles. Research carried out in regard to this topic addresses the relationship of monitoring data for ambient air with personal exposures to PM and gaseous copollutants. Data on this relationship are needed not only for healthy people but also for those persons who are particularly susceptible to air pollution and at greatest risk for experiencing adverse effects. Such persons are referred to collectively as a "susceptible subpopulation" and are further addressed under topic 8 later in this chapter.

State of Understanding in 1997

Before 1997, the majority of time-series analyses of morbidity and mortality data relied on ambient air pollution concentrations as measures of exposure. A critical assumption of these investigations was that ambient PM concentrations serve as surrogates of corresponding personal exposures to ambient particles. Previous findings from personal monitoring studies suggested that human exposures differ from ambient concentrations due to the contributions of microenvironmental sources (Dockery and Spengler 1981; Ozkaynak et al. 1993; Ozkaynak et al. 1996a). In addition, most of these investigations found statistically insignificant and weak associations between personal exposures and ambient concentrations when assessed cross-sectionally (that is, at different locations). However, these conclusions were based on a small number of studies that were originally designed

to determine population exposure distributions rather than to examine the strength of association between personal exposures and ambient concentrations, particularly, over time.

To address this knowledge gap, the National Research Council (NRC) recommended that further research be conducted to characterize longitudinal personal exposures to $PM_{2.5}$, including their relationship to ambient $PM_{2.5}$ and other pollutants (NRC 1998). For these longitudinal studies, groups of individuals would be measured at successive points in time to examine the relationship between their exposures and the corresponding ambient concentrations over time. This recommendation was based on findings from previous studies showing stronger correlations for data analyzed longitudinally rather than cross-sectionally (Lioy et al. 1990; Janssen et al. 1997). Additional objectives of these studies included (1) identifying factors, such as PM spatial and temporal variability, season, meteorology, time-activity patterns, and building characteristics, potentially influencing the observed relationships; (2) recruiting individuals susceptible to the effects of PM exposures, such as chronic obstruction pulmonary disease (COPD) patients, persons with cardiovascular disease or hypertension, older persons, persons with asthma, and children; (3) determining the fraction of ambient particles to which humans are exposed (henceforth, attenuation factor) and investigating its variability across different populations, seasons, climates, and home characteristics; and (4) examining relationships between personal exposures to particles and gases and their respective ambient concentrations and investigating the role of gaseous copollutants in studies of PM health effects.

What Has Been Learned?

Numerous PM exposure assessment studies were conducted in various locations in the United States with different climatic conditions and air pollution mixtures, including Atlanta, Baltimore, Boston, Fresno, Los Angeles, New York, Research Triangle Park, Seattle, Steubenville, and St. Louis. Support for these studies was provided by EPA, the Health Effects Institute, the Electric Power Research Institute (EPRI), the California Air Resources Board, the U.S. Department of Energy, the Ohio Coal Development Office, and the American Petroleum Institute. Studies were also conducted in Europe and South America. Although the exposure assessment studies were undertaken independently by several universities and research organizations, similar sampling and measurement approaches were

adopted with the goal of generating comparable data sets. Collectively, several hundred participants were monitored during periods ranging from 1 to 12 days, generating approximately 20,000-30,000 personal, indoor, outdoor, and ambient samples. The results from the longitudinal PM exposure studies have already yielded new understanding of PM exposure concentrations and factors influencing these exposures and will continue to be critical in the evolution of the PM exposure assessment field.

From 1998 to 2002, more than 40 peer-reviewed papers have been published in scientific journals. Approximately 50 references of the PM criteria document (EPA 2002a) were included in Chapter 5. Topics covered ranged from associations between personal exposures and ambient concentrations (referred to as personal-ambient associations) to quantifying statistical models of exposure and field-method evaluation.

During 1997-2002, a series of longitudinal PM panel studies were conducted. The field operations and laboratory-analysis components of these investigations have been completed; however, data analysis is still under way for many of these studies. Summarized below are the major findings obtained from analyses of the collected data.

Relationship Between Personal Exposures and Ambient Concentrations

Below, the term concentration will be used to refer to measurements obtained from stationary monitors in different microenvironments, such as indoors, outside a home, and at centrally located outdoor sites, whereas the term exposure will be used to refer to personal exposure measurements. Results from the recent panel studies support the hypothesis that ambient $PM_{2.5}$ concentrations are significant predictors of corresponding personal exposures over time for cohorts of children, older persons, and persons with COPD (Ebelt et al. 2000; Evans et al. 2000; Rojas-Bracho et al. 2000; Sarnat et al. 2000, 2001; Williams et al. 2000a,b; Rodes et al. 2001). Several longitudinal exposure assessment studies measured personal PM_{10} exposures and reported weaker personal-ambient associations than between those for $PM_{2.5}$ (Evans et al. 2000; Rojas-Bracho et al. 2000; Williams et al. 2000a; Chang and Suh 2003).

Subject-specific correlation coefficients showed considerable interpersonal variability, from nonsignificant to values approaching unity (Rojas-Bracho et al. 2000; Williams et al. 2000a; Wallace et al. 2002). Home air exchange rate (AER) as well as AER surrogates, such as air conditioning

use, open window status, season and climatic conditions, were found to be important factors explaining variability in the strength of the correlations (Long et al. 2001a; Howard-Reed et al. 2002; Wallace et al. 2002). Personal-ambient associations were found to be stronger for participants residing in homes with high AERs (Rojas-Bracho et al. 2000; Sarnat et al. 2000). The strength of the personal-ambient associations for $PM_{2.5}$ and PM_{10} increased as the number of repeated measures per individual increased from a few days up to 15 days (Williams et al. 2000a).

Several monitoring studies have investigated the spatial variability of ambient PM concentrations. Studies conducted in eastern locations, such as Boston, New York, Philadelphia, Atlanta, and Research Triangle Park, found that ambient $PM_{2.5}$ concentrations are homogeneously distributed throughout these metropolitan areas, as shown by high cross-city $PM_{2.5}$ correlations (Wilson and Suh 1997; Lippmann et al. 2000; Williams et al. 2002). In contrast, monitoring studies of coarse particle concentrations have shown considerable spatial heterogeneity (Burton et al. 1996; Evans et al. 2000; Chang and Suh, 2003; Goswami et al. 2002; Zhu et al. 2002). Greater variability in $PM_{2.5}$ concentrations was observed in two western U.S. cities, Los Angeles and Seattle. In Los Angeles, $PM_{2.5}$ concentrations measured at coastal monitoring sites were significantly lower than those measured inland (Chang and Suh 2003). Likewise, results from an exposure study in Seattle showed that $PM_{2.5}$ concentrations decreased with increasing elevation (Goswami et al. 2002). Despite those findings, the generally strong personal-ambient $PM_{2.5}$ correlations reported in the longitudinal exposure assessment studies downplay the importance of spatial variability of ambient $PM_{2.5}$ as a modifier of personal-ambient relationships (Wilson and Suh 1997).

There is also evidence that specific sizes or components of $PM_{2.5}$, especially those associated with mobile-source emissions (for example, elemental carbon and ultrafine particles), might exhibit a greater degree of spatial variability and, correspondingly, weaker personal-ambient correlations (EPA 2002b). Pellizari et al. (1999), using a probability sample study design, showed that the mass fraction of $PM_{2.5}$ manganese (a gasoline additive in Canada) varied spatially across the Toronto metropolitan area, significantly altering the observed personal-ambient correlations. Ultrafine ratios outside and inside homes were noted to be highly variable in Fresno homes, and local outdoor combustion sources were noted to contribute highly to this variability (Lawless et al. 2001; Vette et al. 2001). Ultrafine particle concentrations were shown to be highest near highways in Los Angeles and to drop to background concentrations within 300 meters (m)

of the highway (Zhu et al. 2002). Therefore, personal-ambient relationships for specific particle components and size fractions are expected to differ from those observed for $PM_{2.5}$. This hypothesis should be investigated in future studies, as suggested by research topic 2.

Collectively, the panel studies, which were performed on various cohorts (several hundred individuals) and cities across different seasons, showed that there were varying degrees of association between personal exposures and ambient concentrations for the measured individual, with almost half of the associations being nonsignificant. In general, the percentage of participants with significant associations for PM_{10} was less than that for $PM_{2.5}$ (Sarnat et al. 2000; Williams et al. 2000a,b). The personal-ambient associations involving exposures to particles primarily of ambient origin (SO_4^{2-}) were shown to be consistently stronger and less variable than those found for $PM_{2.5}$ (Ebelt et al. 2000; Sarnat et al. 2000; Landis et al. 2001; Brown et al. 2003). These findings highlight the influence of nonambient $PM_{2.5}$ contributions on personal exposures and the weakening effect of these contributions on associations of personal exposures with corresponding ambient $PM_{2.5}$ concentrations (Rea et al. 2001).

Indoor Concentrations

Individuals spend their time in a variety of microenvironments, such as the home, workplace, school, in transport media, and outdoors. To date, however, most microenvironmental studies have focused on ambient and residential microenvironments. For that reason, this discussion focuses on the residential and outdoor environments; for simplicity, the terms indoor and ambient will be used to refer to these two microenvironments, respectively. Studies referenced in this discussion used measurements conducted either outside homes (outdoor concentrations) or at a centrally located fixed site (ambient concentrations). For brevity, the term ambient concentrations will be used for both ambient and outdoor concentrations.

Near-real-time $PM_{2.5}$ indoor and personal measurements have highlighted the importance of microenvironmental PM sources (Abt et al. 2000; Howard-Reed et al. 2000; Long et al. 2000; Rea et al. 2001; Vette et al. 2001). However, there is no evidence that indoor exposures have a strong effect on personal-ambient relationships. This lack of effect may be explained by the patterns of contributions of indoor sources to personal exposures to particles. Although indoor source use may be intermittent, the daily patterns of use are relatively consistent. Therefore, when indoor PM-

source contributions are averaged over repeated 24-hour (hr) sampling periods, they add only a small fraction to total $PM_{2.5}$ exposure variability for a particular person over time. That result might not be true for locations where ambient concentrations are very low or individuals are heavily exposed to specific microenvironmental sources (for example, cigarette smoking).

Particles of indoor origin can be produced either by combustion sources, such as cooking or gas phase reactions (mostly ultrafine particles), or by mechanical processes, such as vacuuming, sweeping, or dusting (mostly coarse particles). In contrast, most particles of ambient origin found indoors are present in the accumulation mode, because the penetration of ultrafine and coarse particles is considerably lower than that of particles in the accumulation mode (Long et al. 2001a; Vette et al. 2001). The fraction of ambient particles that penetrates indoors varies considerably (from approximately 0.3 to 1.0), and it increases with the home AER (Sarnat et al. 2002). The infiltration efficiency in 44 homes in Seattle varied from about 0.3 to 1.0 and was a function of AER (Allen et al. 2003; Wallace et al. 2004). In addition, the average infiltration factor for 294 homes of inner-city children with asthma in several U.S. cities was found to be 0.50 (Wallace et al. 2003). Finally, the relative impact of ambient and indoor sources has also been shown to depend strongly on the home AER and removal processes, such as filtration by forced air heating, ventilation, or air-conditioning or by independent air cleaners (Rodes et al. 1998).

Impact of Ambient Concentrations on Personal Exposures

Until recently, the variability in personal PM exposures was considered to be primarily due to the contributions from microenvironmental sources; all PM particles of ambient origin were also considered to penetrate indoors. There is now strong evidence, however, that a substantial fraction of this variability is due to the impact of ambient sources on the indoor environments and, subsequently, on personal exposures (Landis et al. 2001; Williams et al. 2002). The fraction of ambient PM concentrations to which individuals are exposed (attenuation factor) has been shown to vary considerably. For example, in Baltimore during the summer, the estimated average attenuation factor for two investigated cohorts (children and older persons) was 0.48, which was substantially lower than that estimated for Boston during the same season and for the same cohorts (0.81). The average attenuation factor for these cohorts during the winter-

time season for Baltimore and Boston were similar, 0.23 and 0.27, respectively (Brown et al. 2003). Analysis of similar data sets from different locations will probably provide more information about the variability of this factor and the parameters influencing its variability (that is, home ventilation characteristics and time-activity patterns) (Rodes et al. 2001). Finally, future studies should focus on characterizing attenuation factors for specific PM components and size fractions (research topic 2).

Particles of Ambient and Indoor Origin

Associations have been found between mortality and morbidity outcomes and corresponding ambient PM concentrations, suggesting an adverse effect of exposures to ambient PM. However, studies have suggested that PM of indoor origin might be associated with adverse effects (Drumm et al. 1999; Long et al. 2001b). These studies point to the need for a comprehensive assessment of exposures to particles of both ambient and indoor origin, in part to make possible the assessment of the individual effects of both particle types.

The relative contributions of ambient and indoor PM sources to personal exposures were investigated in recent studies using different approaches. For example, sulfate was used as a tracer of ambient PM (Wilson and Suh, 1997; Ebelt et al. 2000; Oglesby et al. 2000; Sarnat et al. 2000; Landis et al. 2001). Although sulfate is a suitable tracer for the accumulation mode, it might overestimate the penetration of ambient ultrafine and coarse particles indoors. Alternatively, statistical methods based on the regression of personal exposures or indoor air concentrations on ambient concentrations have also been used (Ott et al. 2000; Wallace and Ott 2002).

Cohort Effect

When the longitudinal exposure studies were initiated, personal exposures to PM were hypothesized to differ by subpopulation because of time-activity differences. The EPA National Exposure Research Laboratory (NERL) measured $PM_{2.5}$ exposures of two distinct subpopulations living within the Research Triangle Park (RTP) region of North Carolina (Williams et al. 2002). A total of 38 participants were monitored (a cohort of 30 nonsmoking, hypertensive African-Americans living in a low-to-moderate

socioeconomic status neighborhood of Raleigh and a multiracial cohort of 8 individuals with implanted cardiac defibrillators from Chapel Hill) (Wallace et al. 2004). Contrary to expectations that the multiracial cohort with implanted cardiac defibrillators might be more sedentary than the hypertensive African-American cohort, analysis of the time-activity patterns did not show statistically significant differences between the two groups. Considerable intracohort variability was found, however, in the duration and location of activities conducted.

Brown et al. (2003) found no differences in exposures to $PM_{2.5}$ of ambient origin among the investigated cohorts of children, COPD patients, and healthy older citizens living in Baltimore and Boston. Personal $PM_{2.5}$ exposures were measured for 56 subjects living in Baltimore and 43 subjects living in Boston. The Baltimore study investigated 20 healthy senior citizens, 21 schoolchildren, and 15 individuals with COPD. The Boston study investigated 20 healthy older citizens and 23 schoolchildren. (Brown et al. 2003). Using mixed models, the study had personal exposures regressed on the corresponding outdoor concentrations. Both city and season were found to have an effect on the regression intercept (mostly nonambient exposures) and slope (attenuation factor). Similar to the RTP study, no cohort effect on the regression intercepts or slopes was found. These findings were somewhat unexpected considering the hypothesized differences in cohort activities and time spent outdoors during the 24-hr sampling periods.

Exposures to Gaseous Copollutants

In several longitudinal panel studies, simultaneous 24-hr personal $PM_{2.5}$, ozone (O_3), sulfur dioxide (SO_2), and nitrogen dioxide (NO_2) exposures and corresponding ambient concentrations were measured using a personal multipollutant sampler. The findings of these studies suggest that personal $PM_{2.5}$ exposures and corresponding ambient concentrations were correlated, and personal O_3, SO_2, and NO_2 exposures were not correlated with their respective ambient concentrations (Sarnat et al. 2001). In contrast, $PM_{2.5}$ personal exposures were correlated with O_3 and NO_2 ambient concentrations. Similar results using different sampling methods were observed in the Baltimore and RTP panel studies (Williams et al. 2000c; Vette et al. 2002). These results suggest that using ambient gaseous concentrations in multipollutant health-effects models along with $PM_{2.5}$ might not be appropriate, since the ambient gaseous and $PM_{2.5}$ concentrations are serving as surrogates for $PM_{2.5}$ exposures.

How Much Has Uncertainty Been Reduced?

Over the past 6 years, PM exposure assessment studies of healthy and susceptible individuals have been conducted. During this period, significant progress has been made in reducing methodological uncertainties in the assessment of gravimetric PM mass (Allen et al. 1999; Lawless and Rodes 1999) and in the PM monitoring methods used in personal exposure assessment (Williams et al. 2000b; Demokritou et al. 2001). Studies characterizing exposure among sensitive populations, in particular, directly addressed a major research need identified by this committee. The results show that the relationship between personal exposures and ambient concentrations varies considerably both within and between the measured cohorts. The observed dissimilarities among individuals were attributed to differences in home characteristics, which likely vary by season and region, and, to a lesser extent, time-activity patterns and microenvironmental sources. Although analysis is still being conducted to examine potential cohort-specific exposure patterns, results to date do not indicate significant differences in $PM_{2.5}$ exposures among the cohorts (Brown et al. 2003; Wallace et al. EPA, unpublished material, 2003; Williams et al. 2002).

Despite the interpersonal differences observed within each of the investigated panels, significant associations between personal and ambient concentrations were found for approximately one-half of the measured individuals (Sarnat et al. 2001; Liu et al. 2003). Although these results are based on a small number of individuals who might not be representative of the entire population, they suggest that the use of $PM_{2.5}$ concentrations as a surrogate of population exposures is a reasonable and scientifically sound assumption. However, the conclusions drawn for $PM_{2.5}$ might not be applicable to other particle-size fractions, such as ultrafine and coarse particles, and particle components (for example, elemental carbon, metals, and organic compounds). Future research, outlined in research topic 2, will focus on the exposure assessment of different particle-size fractions and constituents.

As mentioned above, considerable intrapersonal and interpersonal variability was reported in the relationships between personal $PM_{2.5}$ exposures and corresponding ambient concentrations. In the past, these differences were attributed to the impact of microenvironmental sources. However, the recent findings provide compelling evidence that the fraction of ambient particles penetrating indoors might be highly variable, thus weakening personal-ambient associations. The recent studies suggest that the

fraction of ambient particles affecting personal exposures varies by location and season, especially in cities where distinct seasonal weather patterns exist. Therefore, it is reasonable to assume that differences in observed risks in multicity epidemiological studies can be attributable, in part, to corresponding differences in the contributions of ambient PM sources to personal PM exposures (Janssen et al. 2002).

Emerging information from multipollutant exposure studies suggests that ambient concentrations of gaseous pollutants, such as O_3, SO_2, and nitrogen oxides (NO_x), in some U.S. cities are associated with personal $PM_{2.5}$ exposures and not with personal exposures to the gases themselves (Williams et al. 2000d; Sarnat et al. 2001; Brown et al. 2003; Vette et al. 2002;). (No results are available for carbon monoxide (CO), however, because short-term or continuous personal exposure measures are not available for this pollutant gas.) Therefore, a number of ambient gaseous copollutants might be surrogates of fine-particle personal exposures and not confounders of associations of PM with outcome measures. This information is relevant to the development of multivariate statistical models that include PM and other pollutants and also to the interpretation of model findings. This methodological issue receives further consideration in research topic 10.

Synthesis

The longitudinal exposure assessment studies conducted during the past 6 years have provided support for findings reported in the time-series epidemiological studies that use ambient concentrations as surrogates of personal exposures. For about half the measured individuals, ambient concentrations were shown to be significantly correlated with corresponding personal exposures.

Scientific Value

The design and execution of the longitudinal exposure assessment studies were largely successful. These investigations comprised measurements of different cohorts living in a variety of climates and locales and exposed to varying levels of ambient pollutants. The information obtained from these studies has enhanced the understanding of the relationship

between ambient PM concentrations and corresponding personal exposures—ambient PM concentrations have been shown to correlate well with personal PM exposures for a substantial fraction of the measured individuals over time. These investigations have produced a large number of publications in various peer-reviewed journals and have been extensively cited in the most recent version of the criteria document for the PM NAAQS.

A large PM exposure data set has been collected and continues to be analyzed. To date, study findings have been used to validate acute-exposure epidemiological study results. In the future, data from these studies will also be used to develop retrospective and prospective estimates of PM exposures for chronic epidemiological studies.

Decisionmaking Value

A great number of issues were raised during the previous PM NAAQS review. Findings from the exposure assessment studies are relevant to addressing several of those key issues:

1. Risks for susceptible populations as compared with healthy individuals.
2. Potential effects of gaseous copollutants.
3. Validity of acute-exposure time-series epidemiological studies, particularly the consequences of measurement error.
4. Relative toxicity of ambient and indoor PM.

An understanding of human exposures to particles of ambient origin makes it possible to directly link the impact of an ambient air quality standard on personal exposures to ambient particles. As discussed above, recent findings suggest that the relationship between exposures to particles of ambient origin and the corresponding ambient concentrations can vary by season, location, and home characteristics. The variation implies that a single nationwide PM standard may provide a different degree of protection for different populations, depending on season, regional home characteristics, and indoor ventilation patterns.

Initial results describing the relationship between personal PM exposures and the corresponding ambient concentrations of gaseous copollutants may also be critical for efforts to elucidate the role of gases. To develop scientifically sound and cost-effective particle standards, it will be neces-

sary to determine the effect of gaseous pollutant exposures on the PM exposure-response relationship.

Information Expected in the Near Future

A rich data set on particle human exposures has been collected since 1998 as part of the recommended longitudinal exposure assessment studies. These studies have generated a wealth of data on personal exposures, indoor concentrations, home characteristics, time-activity patterns, and outdoor concentration spatial patterns. To date, analyses of these data have generated a large number of reports and peer-reviewed publications; however, these databases have not yet been fully explored. Researchers will continue mining these data for at least the next 5 years. Of particular importance is the potential use of these data in developing chronic PM exposure models. Furthermore, studies characterizing exposures to specific PM components are planned or are being conducted and will enhance the understanding of the relative impact of these components on human health. Finally, analysis of real-time PM concentration data will provide the means to calculate the contribution of various indoor sources to total personal exposure and clarify the definition of personal particulate clouds.

Major Remaining Uncertainties

It is important to compare the initial findings, reported above, to the results from the upcoming data analyses. As mentioned above, an effort was made to use similar sampling methods and survey tools for the majority of studies, making it possible to analyze the results collectively. The application of an identical statistical approach to the entire database will allow a better comparison across cities, seasons, cohorts, home characteristics, and other exposure modifiers already identified by the different investigators. Finally, it will be necessary to develop a statistical framework that will make it possible to examine whether the results from the panel studies apply to the general population.

What Remains To Be Done?

Although substantial data have been collected, they are not sufficient

to develop a national perspective on the relationship between ambient PM concentrations and personal exposure, because there is a lack data from a set of fully representative persons and locations. Also, there is very little information about the exposures of susceptible individuals to particles and other air pollutants. Further studies on such individuals are needed, particularly those at the highest risk for mortality. In terms of the timing of further exposure assessment studies of susceptible individuals, they might be deferred until monitoring techniques could provide insight into exposures to specific components of PM and further progress is made in assessing hazardous components of PM (topic 5).

In addition, the following specific research objectives should be pursued:

- Complete the analyses of data collected as part of the $PM_{2.5}$ panel exposure investigations and provide the resources necessary for integration and generalization of the results.
- Use existing $PM_{2.5}$ data from the panel exposure studies to evaluate existing chronic and acute exposure models and develop new models when necessary.
- Use the evolving computational tools for geographical mapping in exposure assessment and epidemiological investigations of particulate matter.
- Conduct a series of multipollutant exposure studies to confirm recent findings on the relationships between gaseous and particulate pollutants for personal and ambient exposures.
- Use personal exposure measurements and models to quantify the effectiveness of emission-control strategies in reducing particle exposures. These investigations would focus on populations at high risk before and after implementation and would provide a more accurate exposure metric than ambient data would provide in assessments of accountability.
- Investigate the composition, size, and toxicity of particles of nonambient origin contributing to personal exposures.
- Develop distributions on home ventilation, particle penetration, and particle deposition values for different geographical regions and seasons.
- Conduct new exposure studies for coarse and ultrafine particles, including time and spatial patterns of ambient concentrations and characterization of personal exposures.
- Determine the contribution of potential causal agents (sources) to the total personal exposure of general and susceptible populations.

RESEARCH TOPIC 2
EXPOSURES OF SUSCEPTIBLE SUBPOPULATIONS TO TOXIC PARTICULATE MATTER COMPONENTS

What are the exposures to biologically relevant constituents and specific characteristics of particulate matter that cause responses in potentially susceptible subpopulations and the general population?

Introduction

Research topic 2 extends research topic 1, shifting the emphasis on exposures to specific types of particles that have been found to be associated with greater risk for health effects. In the committee's portfolio, research related to topic 2 would be implemented only after understanding the characteristics of particles and assessing hazardous PM components, as discussed below under topic 5.

State of Understanding in 1997

Before 1997, very little information existed on particle exposures with characterized chemical composition and size characteristics. There has been a need to expand the database on exposures to particles in relation to the characteristics of the particles, particularly those considered to convey toxicity.

What Has Been Learned?

The committee highlighted the need to characterize the physical and chemical properties of particle exposures for the general public and susceptible subpopulations. Specifically, population-based field studies would provide information on the distribution and intensity of exposure for defined components and specific size fractions. Longitudinal studies would also investigate the relationship between personal exposures and ambient concentrations for specific components and particle-size fractions. Toward that end, the committee suggested that state-of-the-art personal exposure measurement methods be developed and implemented. Comprehensive and cost-effective field studies will then be designed to determine population

exposures based on the results from the longitudinal panel studies (topic 1).

To date, the research conducted on exposures to the toxic components of PM has focused on development of methods and applications of speciation techniques within a small number of exposure studies. These efforts will be useful in initial chemical characterizations of exposure and in the design of future exposure studies. However, these techniques can be fully implemented only in exposure studies after ongoing and future toxicological studies identify components of biological relevance. Specific progress is detailed below.

Sampling Methods

Personal sampling devices have been developed and field tested. These methods make it possible to obtain information on personal exposures to different particle fractions and their components. More specifically, new methods have been developed for PM_{10} and $PM_{2.5}$, elemental and organic carbon, ionic species, elements, elemental and organic carbon, and organic compounds (Demokritou et al. 2002). In addition, new personal sampling devices allow for the simultaneous collection of gaseous copollutants, $PM_{2.5}$ and PM_{10}, and particle composition (Chang et al. 1999; Demokritou et al. 2001). The development of new sampling and analysis protocols in conjunction with the use of more sensitive analytical techniques has made it possible to improve measurement precision and accuracy. One of these advancements has been the ability to decrease the sampling flow rates and, therefore, reduce the size of the personal sampling devices.

Personal Measurements of Particulate Mass and Its Components

As discussed under topic 1, real-time measurements of fine mass and ultrafine particles have been conducted and have demonstrated the importance of nearby sources in determining total personal exposures (Fischer et al. 2000). These measurements will be critical to efforts in identifying sources that contribute to personal exposures and link exposures to specific activities or events. In addition, state-of-the-art studies on exposure health effects conducted simultaneous real-time personal exposure and biological monitoring (Liao et al. 1999; Howard-Reed et al. 2000). That was done to link magnitude and duration of exposures to biologically relevant events.

Specifically, the relationships between real-time fine particles and adverse cardiac functions have been examined.

A small number of studies have conducted measurements of personal exposures to various particulate constituents, including sulfate, nitrate, ammonium, elemental and organic carbon, and elements (Ebelt et al. 2000; Sarnat et al. 2000; Williams et al. 2000a,b,c). Such studies enable investigation of the relationships between personal exposures to specific particle constituents and the corresponding ambient concentrations.

What Remains To Be Done?

Although monitoring methods are being developed for the goals of topic 2, the uncertainties associated with the topic remain largely unaddressed. The committee's sequence of research calls for more substantial advances under topic 5 before fully implementing topic 2. Exposure studies will be necessary for particle components of biological relevance. These investigations should examine the relationships between those personal exposures and the corresponding ambient concentrations for susceptible subpopulations and the general public. Some of the studies should characterize exposure distributions for a variety of microenvironments, including work, school, and transportation environments.

RESEARCH TOPIC 3
CHARACTERIZATION OF EMISSION SOURCES

What are the size-distribution, chemical-composition, and mass-emission rates of particulate matter emitted from the collection of primary-particle sources in the United States, and what are the emissions of reactive gases that lead to secondary- particle formation through atmospheric chemical reactions?

Introduction

A large variety of emission-source types, both natural and artificial, are responsible for PM in the atmosphere. These emission sources directly emit PM (primary particles) that over time becomes coated with the low-vapor-pressure products of atmospheric chemical reactions (secondary

particles) involving O_3 and other oxidants, SO_2, NO_x, ammonia (NH_3), and volatile organic compounds (VOCs). Secondary particles can also be formed through the reaction of gases by themselves. Natural sources that contribute to ambient PM include wind erosion, forest fires, sea salt spray, and biological processes in plants and soils. There are several hundred different emission source types in urbanized areas, such as mobile sources, stationary-source fuel combustion, industrial processes, and area-wide sources.

Knowledge of the size-distribution, chemical-composition, and mass-emission rates of the many sources of primary PM and secondary PM precursors is basic to health hazard assessment and effective regulation. In terms of the research effort that forms the basis for setting NAAQS, knowledge of the characteristics of emitted particles is needed by laboratory toxicologists to choose particle exposure systems (topic 5) that accurately represent the relevant differences in the particles emitted from the many different source types. Confidence in the air quality simulation models (topic 4) and emission-control strategies that will be used to implement the PM NAAQS over this decade will depend, in great measure, on the ability to specify emissions accurately.

In its second report (NRC, 1999), the committee noted that traditional emission inventories focused on representing PM mass emissions, and it created a set of research recommendations that address measurement of the size distribution and chemical composition of PM emissions from sources. Characterization of the emission rates of reactive gases that can form particles upon reaction in the atmosphere was also emphasized. Because studies on particle toxicology are ongoing and air quality simulation models are needed within the next several years to meet projected regulatory schedules for state implementation plans, the committee called attention to the need for the research to begin immediately.

This section reviews progress based primarily on the peer-reviewed scientific literature and emission-inventory procedures adopted by regulatory agencies.

State of Understanding in 1997

As described in the 1996 PM criteria document (EPA 1996), the national emissions inventory was limited to mass emissions for PM_{10}, SO_2, NO_x, and VOC, and there were few size-resolved (for example, $PM_{2.5}$) emission estimates and chemically speciated emission estimates. A national

NH_3 inventory did not exist. Emission uncertainty estimates were limited to VOC and CO emissions from on-road passenger cars.

Seminal research efforts by G. Cass (see p. viii) and his coworkers developed the first size-resolved, chemically speciated emissions inventory for PM and PM precursors and successfully simulated the processes that result in observed concentrations of sulfates, nitrates, and carbonaceous species in the Los Angeles airshed. However, even in Los Angeles, there were major uncertainties in PM emissions from gasoline- and diesel-fueled vehicles. For example, heavy-duty diesel trucks were estimated to be the largest single source nationwide of combustion particles and NO_x, but the emissions inventory was based on tests of only 70 trucks (versus 6000 tests of NO_x and VOC emissions from light-duty gasoline vehicles), and many of these used outdated engine-test procedures, rather than chassis dynamometer tests, and unrepresentative driving cycles (Lloyd and Cackette 2001). In addition, this research did not include ultrafine particle emissions (less than 0.1 micrometer [μm] in aerodynamic diameter) or sources that are predominant in other parts of the United States (for example, coal-fired power plants).

In light of the need for data on the size and chemical composition of particle emissions from sources, the committee's second report (NRC 1999) outlined the following set of research needs:

- Establish standard source-test methods for measurement of particle size and chemical composition.
- Characterize primary particle size and composition of emissions from the most important sources.
- Develop new measurement methods and techniques for using the data to characterize sources of gas-phase ammonia and semivolatile organic vapors.
- Translate new source-test procedures and source-test data into comprehensive national emission inventories.

Those broad research needs also align with emissions characterization recommendations from the recent North American assessment of PM atmospheric science (NARSTO 2003).

What Has Been Learned?

The committee reviewed research progress on the basis of its emissions characterization recommendations in its third report (NRC 2001).

Although more work has been published since 2001, the areas with and without progress are largely unchanged. Much of this research is focused on motor vehicles and not the comprehensive suite of resources that need attention for national inventories. Except for a national multisponsor effort to quantify emissions from heavy-duty diesel trucks, a recent EPA-organized effort to assess particle emissions from on-road light-duty gasoline vehicles and several pockets of excellence within EPA (for example, biogenic emission assessment), the research has not been implemented at the scale, timing, quality, and integration envisioned in the committee's second report (NRC 1999). Overall, a strong, cohesive emissions characterization research program has not emerged within the PM research agendas of EPA, the states, or other research sponsor organizations. The lack of a specific focus on PM emissions characterization in EPA's extramural funding programs might be partially responsible for the persistence of substantial knowledge gaps.

One measure of progress in addressing the committee's recommendations is the number of emission-related peer-reviewed scientific publications since 1997. An early 2003 literature search produced about 330 journal articles (230 articles from the United States) reporting wholly or in large part on PM and PM precursor emissions that were published during 1997-2002. Because much emissions research is conducted by consultants who tend to report results in the "gray" literature (for example, final reports to the sponsoring organization and conference proceedings), these peer-reviewed publications represent a substantial total research output and one that would represent an adequate overall level of effort if focused on the committee's recommendations. However, about 40% of the articles focused on motor vehicles and were inadequate for the committee's specific recommendations in most of the other emission-source types.

The U.S. journal articles primarily reflected the work of about 30 research institutions, reflecting the specialized nature of the facilities and equipment required for emissions characterization. In addition to EPA, about 10 major U.S. organizations were involved in sponsoring such research, providing an opportunity for EPA to leverage its limited funds. The literature was not dominated by any single research organization or funding source, although EPA was the single largest sponsor. The research output was lower in 1997 and 1998 and uniform from 1999 to 2002, reflecting the increased resources EPA and other sponsoring organizations invested in emissions characterization since the promulgation of the $PM_{2.5}$ NAAQS in 1997. Several papers dealt with more than one source type; thus, the following categories and percentages include overlapping citations. About 30% of the papers dealt with emission factors (the second recommendation

within this topic, as mentioned above) for mobile sources, reflecting the importance of passenger car and heavy-duty diesel vehicle contributions to $PM_{2.5}$ concentrations, as well as the priority of sponsoring organizations. There were about 55 papers on heavy-duty diesel vehicles and another 40 on passenger cars, but only one paper addressed brake- or tire-wear, two significant motor-vehicle sources that have not been well characterized. There were less than 10 papers each on other important primary PM sources (aircraft, biomass combustion, industrial sources, power generation, watercraft, and windblown dust); thus, many critical source types have only been studied by the research of Cass and associates in the mid-1990s or not addressed at all. Another 40 papers focused on gas-phase ammonia and semivolatile organic vapors (third recommendation within this topic). There was only one paper on a comprehensive emissions inventory (fourth recommendation within this topic) and one on ultrafine PM emissions for the Los Angeles air basin (Cass et al. 2000), but there were 15 papers on characterizing emission-inventory uncertainty for specific sources types (for example, Frey and Bammi 2002; Frey and Zheng 2002).

Another measure is the incorporation of research results in emission-inventory procedures and the availability of a comprehensive emission inventory for air quality model testing. There is a substantial lag between the generation of new results from emission research and their incorporation into EPA's emission procedures. For example, most of the papers identified above are not cited in the Emission Inventory Improvement Program (EIIP), an EPA, state, and local collaboration to develop consensus emission procedures for air pollutants, including PM and its precursors. Since 1997, EPA has published a national $PM_{2.5}$ emissions inventory (EPA 2000) but has not yet published the chemically speciated inventory necessary for NAAQS implementation. EPA has also developed a national emission inventory for ammonia, but several key sources (for example, natural sources, open burning, and humans) are not included. Given the large gaps in emissions characteriziation for the various sources, the inventory contains substantial uncertainties.

The committee recognizes that EPA and other organizations have formed groups to coordinate research on atmospheric processes in general and specifically on emissions inventory, modeling, and monitoring. Examples of such groups include subcommittees of the State and Territorial Air Pollution Program Administrators and the Association of Local Air Pollution Control Officials (STAPPA/ALAPCO), the Air Quality Research Subcommittee of the Committee on Environment and Natural Resources (CENR), (NARSTO) (originally the North American Research Strategy for Tropospheric Ozone), and the Emission Inventory Improvement Program

(EIIP). NARSTO recently published an assessment of the state of the science and the needed research for PM, including emission inventories (NARSTO 2003). In addition to EPA, other sponsors of emissions-related activities included the California Air Resources Board, Coordinating Research Council, U.S. Department of Energy, U.S. Department of Agriculture, and U.S. Department of Defense.

Decisionmaking Value

Arguably, the greatest policy-relevant advance in the understanding of PM emissions since the last PM criteria document has been the significant improvement in estimates of on-road mobile-source emissions of PM mass, ultrafine particles, ammonia, and semivolatile organic vapors. A national multisponsor effort, involving EPA, implemented standardized test methods for heavy-duty vehicles (Gautam et al 2002) and conducted an intercomparison study of all emission-testing facilities in the United States. The research addressed the effects of changes in fuel composition, operating conditions, and after-treatment devices (for example, catalyzed particle trap); the findings informed recent regulatory decisions by EPA and California Air Resources Board (CARB). The finding that catalytically controlled passenger cars are a major source of ammonia emissions in urban areas is leading to much improved ammonia emission inventories and new research efforts to look at catalyst formulations that minimize these emissions.

Another important advance is the understanding of the composition and size evolution of ultrafine particles from heavy-duty diesel vehicles and, to a lesser extent, light-duty gasoline vehicles. The findings will inform toxicological studies of ultrafine particles. An example of a policy-relevant advance in the understanding of PM and PM precursor emissions from major stationary sources, such as electric power plants, is the increased availability of SO_2 and NO_x data from continuous emission monitors (CEMs).

Decisions about alternative emission-control policies should be based on an accurate understanding of the relative strength and possible toxicity of emissions from various sources. Accurate emission inventories are fundamental to the decisionmaking process. Although there is scientific merit in the work that is under way to develop new source-test methods, the potentially important benefits to the decisionmaking process of more-complete and accurate knowledge of particle emissions evaluated according to size and composition can be realized only if EPA proceeds to expand its

present source-testing program substantially, in accordance with the committee's recommendations.

What Remains To Be Done?

Several of the issues described as inadequately addressed in the committee's third report (NRC 2001) generally remain so at this time. Some progress is being made in the four areas recommended above; however, overall research has not been implemented at the scale, timing, quality, and integration level envisioned in the committee's second report. Comprehensive emission inventories needed for the development and testing of air quality models (topic 4) appear to be lacking, especially for organic carbon. EPA's national emission inventory for ammonia is missing several key sources (e.g., natural sources, open burning, humans) (Pace 2002). Improvements are needed to the estimation of ammonia emissions in order to improve the ability of air quality models to represent nitrate concentrations. Since 1997, only 16 new source profiles have been added to EPA's receptor modeling library, although EPA is now leading a comprehensive update. In the dozen or so source types identified in the committee's second report, research on improved mass emission estimates and chemical speciation is proceeding or planned in just a few areas (for example, heavy-duty diesel trucks, light-duty gasoline vehicles, and animal husbandry). In addition, many aspects of the PM emissions inventory effort lack the comprehensive planning process the committee envisioned, and emissions will likely be a major uncertainty in the implementation of the $PM_{2.5}$ NAAQS. A national emissions inventory is being developed, although EPA indicates that states, local air districts, and Indian tribes are not likely to commit to the detailed information necessary to generate the size and chemical speciation, as well as the spatial and temporal resolution that the committee envisioned.

Although the committee could identify some specific advances in relation to topic 3, a comprehensive, cohesive emissions characterization research program, as recommended by the committee in its second report (NRC 1999), has not been implemented by EPA or other research sponsors, including the states. A leadership role by EPA in relation to this topic is needed, even if some of the necessary emission characterizations will be carried out by states, industry, and other stakeholders. EPA has assumed this responsibility in several important areas: EPA-led programs are updating speciation profiles for receptor-oriented models, assessing particle emissions from on-road light-duty vehicles, and assessing the state-of-the-science and needed research for emission inventories.

Additional standardized test methods need to be developed for the many sources, other than motor vehicles, that contribute major fractions of ambient PM (for example, residential wood combustion, wildfires, cooking, and nonroad engines). These methods should be defined in terms of performance rather than design specification to encourage application and innovation. Hundreds of source compliance samples are taken every year for permit requirements, and more flexible and realistic measurement methods would enhance the value of these tests for multiple purposes, including research and regulatory decisionmaking.

PM_{10} emission source-testing methods overestimate mass emissions from stationary sources by adding mass condensed in impingers to the mass collected on a hot, in-stack filter. The impinger mass is dominated by dissolved gases instead of captured particles, and the hot filter allows condensable material to pass through it. A new $PM_{2.5}$ emission-testing method is needed that dilutes samples to ambient temperature conditions and allows for the addition of multiple filters and particle-sizing instruments. That will supply more realistic estimates of primary particle emission rates, as well as options for obtaining source size distributions and chemical profiles.

Continuous emission monitors on major stationary sources provide the best emission estimates for SO_2 and sometimes for NO_x, but better interfaces are needed to facilitate effective use of this information. CEMs for primary particle emissions should be added where possible.

Although some progress has been made in developing test methods for motor vehicles, methods also need to be developed and applied to better quantify PM and precursor emission rates from in-use engines operating in on-road and nonroad environments. Emission factors based on the CO_2 concentration in exhaust streams can be measured by on-board, in-plume, or remote-sensing analyzers for NO_x, CO, and hydrocarbons. Analogous systems to measure particle mass emissions and size distributions have been demonstrated, but they need to be further developed, tested, and applied. Deviations between engine compliance tests of a few vehicles on dynamometers and in-use engines, fuels, and operating conditions need to be understood and assessed. High-emitting vehicles and cold-start, off-cycle, and nonroad engine emissions might have PM characteristics that differ substantially from those of the federal test procedure (FTP) certification tests.

Static emission inventories, typical of those used for tracking annual trends, are insufficient for estimating the variability in aerosol properties using air quality models. In addition, emissions from other than anthropogenic sources are poorly estimated.

Common geographic information system (GIS) land-use maps for soil types, uses, vegetation, and roadways need to be assembled for easy access and common usage. Because many emissions are meteorologically dependent, time-specific estimates of temperature, relative humidity, and wind need to be developed for input to emission-generation models. The same meteorological fields used to drive air quality models should be used to support emission simulations. Source profiles of PM and VOCs need to be identified, evaluated, documented, and compiled into databases that can be used to provide speciated emission rates and for receptor model source apportionment.

As the committee emphasized in its third report, EPA should now develop a comprehensive plan for systematically applying new source-test methods to develop a completed comprehensive national emissions inventory based on contemporary source tests of comparable quality. To date, that plan has not been developed, even though delay could hinder the development of state implementation plans.

The first step in planning a future source-test program would involve the systematic creation of a master list of sources that most need testing over a specific period. The timeline for this testing must allow for the incorporation of revised and updated data into an overall emissions inventory of predetermined quality and completeness by the time the next round of PM implementation plans must be drafted.

Additionally, there is a need for more efforts to estimate the uncertainties in emission inventory estimates.

RESEARCH TOPIC 4
AIR QUALITY MODEL DEVELOPMENT AND TESTING

What are the linkages between emission sources and ambient concentrations of the biologically important components of particulate matter?

Introduction

The focus of this research topic is the development and testing of source-oriented and receptor-oriented models that represent the linkages between emission sources and ambient concentrations of the components of PM. Before models can be used with sufficient confidence, the source-oriented and the receptor-oriented approaches must be tested against obser-

vations from intensive field programs. Therefore, the discussion on progress in development and testing of source-oriented and receptor-oriented models is followed by that on progress in ambient $PM_{2.5}$ monitoring.

Source-Oriented Models

Atmospheric models are used for evaluating the response of PM to emissions reduction. In additional to meteorological data, such models require information on the emissions and the atmospheric processes that transform those emissions into ambient concentrations. For $PM_{2.5}$, the formation of particles from gaseous emissions is particularly important. Over the past decade, EPA has developed its major new modeling platform, Models-3. There are two basic versions of Models-3, the framework version and the stand-alone code. EPA is continuing to improve the emission estimates used as input to the models and to carry out some research on the processes that are the basis of the model.

The basic goal of this research topic was to improve the source-oriented models through better representation of the processes that need to be incorporated into atmospheric particulate models. Specific needs identified in the committee's second report were the following:

- Improve the representation of water associated with particles, especially for organics.
- Improve thermodynamic models, especially the representation of organics.
- Improve the representation of secondary organic aerosol formation.
- Develop methods to treat cloud and fog water droplets and the associated aqueous-phase chemistry, including the rate and frequency of conversion of the SO_2 to sulfate and NO_x to nitric acid (HNO_3).
- Improve dry deposition and chemical interaction of reactive gases and particles with different surfaces.
- Improve the subgrid-scale treatment of mixing, and large point sources and the rate at which urban plumes of different origin mix within a given region.
- Improve the formulation of the rate of vertical mixing and venting of boundary-layer air with the free troposphere.
- Include the effects of particulate matter on photolysis rates.
- Improve the modeling of the rate of wet deposition, including the dependence of these processes on the type of meteorological system.

- Determine the effect of large-scale meteorological processes, such as aqueous phase reactions and precipitation scavenging on long-term particulate concentrations.

State of Understanding in 1997

In 1997, EPA focused on developing and deploying a specific configuration of Models-3, the community model for air quality (CMAQ), primarily for modeling O_3. Scientific reviews of Models-3 focused primarily on its ability to provide adequate representations of chemical processes to estimate O_3.[1]

The scientific community had first-generation models to describe atmospheric processes related to modeling PM. However, little testing had been carried out, and a number of important processes, noted in the committee's second report and above, either lacked good representation within the models or had not been sufficiently tested. We noted that the problem of developing understanding of seasonally averaged, regional, size-resolved particle concentrations stood as a key unsolved issue. Our third report (2001) noted that EPA had released Models-3 and that it was beginning to be used, but that little testing had been completed, and development of the particulate component was only beginning.

What Has Been Learned?

A small number of research projects funded from 1997 to mid-2001 were on improving the representation of processes in atmospheric particulate models. The work on CMAQ has been done intramurally at EPA with some limited interaction with other model developers. The number of papers on model development and evaluation in the peer-reviewed literature has not been large and studies of specific atmospheric processes have had little support, as noted in the following sections.

[1]The CMAQ model was released for public use in 1998, with annual releases thereafter. The latest release during this study was in June 2002. The code and documentation can be obtained from the following web sites: http://www.epa.gov/asmdnerl/models3/ and http://www.cmascenter.org/

Nucleation

Nucleation was not mentioned in the committee's previous reports, primarily because it was not thought to be important in an urban setting. However, recent studies have documented nucleation events in major cities like Atlanta, as well as in rural polluted areas and forests (McMurry et al. 2000). Substantial numbers of new particles can also form as fresh combustion emissions are entrained into ambient air (Kittelson et al. 1999). Moreover, on a regional scale, nucleation helps determine the number of particles at the smallest sizes and, together with primary emissions, determines the total particle number concentrations. However, the ability to describe nucleation events in models is still in its infancy. While binary homogeneous nucleation of sulfuric acid particles is now described within models, the power dependence of these rates on $[H_2SO_4]$ and $[H_2O]$ differs between experiments and is not well described by current theory (Ball et al. 1999). Moreover, both NH_3 and the formation of ions can increase the nucleation rate, but experiments have not shown whether current theory is adequate (Korhonen et al. 1999; Weber et al. 1999; Kim et al. 2002). Nucleation of new organic particles has been observed but is poorly understood (McMurry et al. 2000).

Uptake of Water and Thermodynamic Properties of Aerosols, Especially Organics

The thermodynamic properties of aerosols determine their ability to take up water. Before 1997, little was known about how to represent this process for organics in models. This area of research has been very active. Models have been developed to describe the thermodynamics and water uptake of some organic compounds (Ansari and Pandis 2000; Clegg et al. 2001; Asher et al. 2002), methods have been identified to determine the precursors of water-soluble organics (Pun et al., 2000), and the effects of organic films on water uptake have been studied (Xiong et al. 1998; Cruz and Pandis 2000). Nevertheless, these methods have not been applied to predict actual measurements (Dick et al. 2000); hence, the validity of current theories and methods remains unestablished.

Secondary Organic Aerosol Formation

Since 1997, a large number of projects and papers have been directed

toward understanding secondary organic aerosol formation, but the number and the diversity of organics pose a huge target for research. Aromatics are by far the most important source of anthropogenic precursors (Stern et al. 1987) but biogenic compounds can also be important (Pun et al. 2002). The relative importance of primary and secondary organic compounds can vary from place to place and even within a single episode (Turpin et al. 2000), but models have not reproduced that behavior. Because of insufficient testing of existing model capabilities, it is not known whether understanding of these processes is adequate.

Representation of Aqueous Chemistry

The representation of the rate of conversion of SO_2 to sulfate in cloud and fog water is often treated as a bulk process in models, despite evidence that the variation of pH with drop size results in different rates in different drop-size ranges. Case studies have continued to demonstrate that although not in all circumstances (Husain et al. 2000; Rattigan et al. 2001; Reilly et al. 2001). Simplified trajectory models can often capture processes in fogs (Lillis et al. 1999), even though drop-size-dependent chemistry is not included. Organic compounds are present in droplets, but their chemistry is not routinely included in models (Herckes et al. 2002), and it is not known whether it should be considered.

Dry Deposition

Dry deposition models perform quite well in daytime conditions over flat, homogeneous terrain, although uncertainties exist in understanding how to scale from the local scale, at which the theory applies, to regional scales. Particle deposition models are available (Zhang et al. 2001), but they rely on empirical scalings that might not be valid for all conditions or on theory that is untested in natural settings (Wesley and Hicks 2000).

Sub-Grid Scale Processes and Vertical Mixing

Research to develop methods to treat reactive plumes has continued (Karamchandani et al. 2000), and methods to treat vertical mixing, especially under stable conditions, have been developed (Sharan et al. 1999). These methods need to be tested within the framework of an Eulerian model and validated against measurements.

Inclusion of the Effects of Particles on Radiation

Including the effects of particles on radiative forcing has been more widely recognized as important over the past several years, but regional air quality models typically do not attempt to include this process. Jacobson (2001) is one exception.

Methods To Determine the Effect of Large-Scale Meteorological Processes on Long-Term Particle Concentrations

At the committee's workshop in March 2002, EPA stated that work was under way to develop methods to predict long-term particle concentrations.

Emission Models

The modeling approach comprises a set of interacting models that begins with the emissions model. The sparse matrix operator kernel emissions (SMOKE) system incorporates several submodels to predict biogenic emissions (BEIS3), mobile sources (MOBILE6b), and several new modules under development to predict fugitive dust, sea spray, and prescribed burning. There have been limited evaluations of these emission submodules.

Models-3

There are two basic versions of Models-3, the framework version and the stand-alone code. Models-3 is just beginning to be deployed and has not yet been extensively tested. A review from a single user of the framework version has indicated it is difficult to set up, but it can be made to function with sufficient effort. EPA has not yet interacted sufficiently with the potential community of users of the framework version, and there does not appear to be ongoing effort to fully support the deployment of the framework to other end users. Thus, although there has been substantial publicity of the framework as a potentially widely used tool, there appears to be considerable additional review and effort needed to make it easily transferable to the end users.

Models-3/CMAQ

The atmospheric science community has had limited interaction with EPA during the development of Models-3. In EPA's response to the committee's earlier questions, EPA suggested that there was limited interaction because the agency faces relatively few major uncertainties about atmospheric processes, and more time is needed before research will provide the needed inputs for the model to produce adequate estimates. However, at the workshop that was held in Research Triangle Park in March 2002 to review progress with respect to topics 3 and 4, the committee was told that now EPA recognized that collaboration is necessary across the scientific community. It is clear from the discussion of atmospheric processes in the previous section that there are a number of areas where further understanding is clearly needed before such processes can be adequately represented in PM models.

In CMAQ, PM is characterized in a limited number of categories, including sulfate, nitrate, ammonium, primary anthropogenic organics, secondary anthropogenic organics, biogenic organics, elemental carbon, other primary, and water. A major concern remains for testing the model. It has been run on relatively few older episodes in the eastern United States. Within this domain, initial evaluation efforts reported to the committee by Schere (2002) suggest an adequate performance in prediction of sulfate mass but an inadequate performance for prediction of nitrate (overprediction) and organic carbon (underprediction) and generally underpredicting overall $PM_{2.5}$ mass. Issues associated with the treatment of organics are summarized above—clearly a key to improving the performance of CMAQ and other source-oriented air quality models is enhancing their treatment. Dennis (2002) concluded that improved ammonia emissions are critical for improving nitrate predictions. A recent evaluation of both CMAQ and REMSAD (Seigneur 2003) has shown poor agreement between model results and measurements for $PM_{2.5}$ mass and three major components of $PM_{2.5}$ (sulfate, nitrate, and organic matter). However, more effort should be made to test the model and to ensure its validity over the entire spatial domain of the United States. In previous reports, the committee suggested the need for a series of major field studies that would provide such data. An effort was made to use the coordinated monitoring done across the eastern United States during July 2001 as part of the Supersites Program, but that is again a limited temporal and spatial domain, and much more will be needed to provide adequate confidence in CMAQ's ability to predict accurately PM and component concentrations.

Other Models

As described in the committee's previous report, EPA has developed a second model, the regulatory modeling system for aerosols and deposition (REMSAD), that is designed to simulate the concentrations and chemical composition of primary and secondary $PM_{2.5}$ concentrations and PM_{10} concentrations and depositions of acids, nutrients, and toxic chemicals. To reduce computational time and costs, REMSAD uses simpler chemistry and physics modules than Models-3. REMSAD has been applied to model concentrations of total $PM_{2.5}$ and $PM_{2.5}$ species (sulfate, nitrate, organic carbon, elemental carbon, and other directly emitted $PM_{2.5}$) over the conterminous United States for every hour of every day in 1990. Annual, seasonal, and daily averages from the 1990 base case have been compared with data from the Interagency Monitoring of Protected Visual Environments (IMPROVE) network and the Clean Air Status and Trends Network (CASTnet). Sensitivity analyses have also been conducted for changes in SO_x, NO_x, ammonia, and directly emitted $PM_{2.5}$. Because of the lack or sparseness of available data on many areas of the United States (for example, IMPROVE provided only two 24-hour-average concentrations per week for a few dozen sites in 1990), there has not been an effective national evaluation of the model for PM. It is not clear whether REMSAD's simplified representations of chemistry adequately capture the complex atmospheric processes that govern observed particle concentrations.

A number of other source-oriented PM models are being developed by individual investigators at universities or consulting companies. Seigneur et al. (1998) reviewed 10 Eulerian grid models: seven for episodic applications and three for long-term applications. The episodic models are the California Institute of Technology (CIT) model, the Denver air quality model (DAQM), the gas, aerosol, transport, and radiation (GATOR) model, the regional particulate model (RPM), the SARMAP air quality model with aerosols (SAQM-AERO), the urban airshed model version IV with aerosols (UAM-AERO), and the urban airshed model version IV with an aerosol module based on the aerosol inorganic model (UAM-AIM). The long-term models are the REMSAD, the urban airshed model version IV with linearized chemistry (UAM-LC), and the visibility and haze in the western atmosphere (VISHWA) model. In addition, several university groups are developing additional PM models that are primarily extensions of the CIT model to other areas of the country.

It appears that none of the models reviewed by Seigneur et al. (1998) is suitable for simulating PM ambient concentrations under a wide range of

conditions. The following limitations were identified in both episodic and long-term models:

- Most models need improvement, albeit to various extents, in their treatment of sulfate and nitrate formation in the presence of fog, haze, and clouds.
- All models need improvement, albeit to various extents, in their treatment of secondary organic particle formation.
- The urban-scale models will require modifications if they are to be applied to regional scales.
- All models but one lack subgrid-scale treatment of point-source plumes.

Chemical-specific modeling and normalization to measured chemical concentrations are major advances in using models to demonstrate an area's plans for attaining the PM NAAQS. These improvements enable a shift away from modeling $PM_{2.5}$ or PM_{10} mass regardless of it composition, as has been the case in the past when SO_2 emissions and fugitive dust would both be assessed on a similar basis regarding their contributions to total mass. Reductions in SO_2 emissions can now be assessed on the basis of changes in sulfate mass rather than the entire PM mass.

Major Remaining Uncertainties

As noted above, progress has been made toward developing accurate representation of processes relevant to the description of atmospheric particles in atmospheric Eulerian grid models. Nevertheless, we found little progress in the following areas:

- Develop methods to treat the rate and frequency of SO_2 conversion to sulfate and NO_x conversion to nitric acid and to nitrate in droplets and fogs.
- Improve dry deposition and chemical interaction of reactive gases and of particles with different surfaces.
- Include the effects of PM on photolysis rates.
- Improve the rate of wet deposition, including the dependence of these processes on the type of meteorological system.
- Determine the effect of large-scale meteorological processes, such as aqueous phase reactions and precipitation scavenging, on long-term PM concentrations.

Excluding the issue of photolysis rates, all the above-mentioned processes need to be incorporated into a large-scale model that includes enough processes to describe most situations adequately. Moreover, it must be fast enough to be able to use it to run a variety of case studies (some of long duration). Although EPA has made a substantial investment in Models-3, it has not been sufficiently tested in terms of its representation of these large-scale, long-time-scale processes.

Receptor-Oriented Models

Source emissions can be linked to ambient concentrations either prognostically, through mechanistic modeling and numerical simulation, or diagnostically, through inferential analysis and mathematical inversion. The prognostic approach is implemented through the use of source-oriented or chemical-transport modeling, which are described in the previous section. These models use known or assumed emission rates, meteorological data, and chemical reaction schemes to derive the concentrations expected to result in the surrounding ambient air. Regulators have historically tended to favor this approach because it takes emissions, the physical parameter most directly affected by their policy decisions, as an explicit input variable for which effects on air quality can be directly explored under any desired scenario. The diagnostic approach, known as receptor-oriented analysis or receptor modeling, begins instead with ambient samples of pollution and uses various forensic techniques to trace them back to their sources. In their temporal variability and their physical and chemical complexity, ambient particles can carry considerable information about their own origins. Although the source-oriented approach is naturally suited to "what-if" analyses, receptor-oriented tools can offer more direct and persuasive evidence of what is.

State of Understanding in 1997

In 1997, the following receptor-oriented approaches were all established analytical strategies at the research level:

1. Detailed speciation of an ambient PM sample to estimate the contributions by categories of emissions having known compositions.
2. Analysis over multiple samples of correlations between chemical

species' concentrations to estimate the compositions of emissions from sources in common.

3. Analysis over time of correlations between concentrations at different locations to estimate source-influence regions.

4. Analysis of air-parcel back-trajectories as a function of observed concentrations to estimate source regions.

Only the first approach, known as chemical mass-balance (CMB) modeling, was recommended by EPA for use in implementation analyses. Most applications of CMB for both regulatory analysis and research used a 1990 package of software and guidance available from EPA. Analyses of types 2-4 were carried out with ad hoc software or general statistical packages.

What Has Been Learned?

EPA has not appreciably increased the overall level of methodological research since the end of 1997, but its monitoring initiatives contribute indirectly to receptor-modeling capabilities. The routine speciation of PM in the Speciation Trends Network, together with the support for developing enhanced particle characterization methods in the Supersite program, will supply some of the routine and advanced ambient data required by CMB and other methods that exploit the information carried by emissions' chemical characteristics. On the other hand, disappointingly little effort has been made to standardize and update the emission measurements and source-characteristics data bases that are equally crucial to the use of such methods.

EPA has supported the development and testing of UNMIX, a sophisticated analytical approach of type 2 (Henry, 2000). To the statistical factor structure that is the basis for the generic approach, UNMIX brings added information in the form of non-negativity constraints on source strengths as well as ambient concentrations. Another refinement of conventional factor analysis has been independently developed in Finland (Paatero and Tapper 1994): Positive matrix factorization (PMF) incorporates measurement error estimates in addition to non-negativity constraints, allowing analyses to include data for species that are undetectable in some samples. Beyond CMB, PMF, and UNMIX, all of which have seen multiple applications by multiple users, new methods continue to introduce new ideas to the mass-balance and factor-analytical approaches (for example, Billheimer 2001; Wiens et al. 2001).

EPA has supported the development of interactive software for CMB and UNMIX that can run under the Windows operating system. A beta-test version and documentation are available for UNMIX (Henry 2000); the new version of CMB is in an earlier stage of development (EPA 2003b).

Several collaborations between proponents of different receptor-oriented tools have taken place since 1997, significantly clarifying the capabilities and limitations of the overall approach (Pitchford et al. 1999; Poirot et al. 2001; Willis 2001). These investigations have estimated source contributions to PM sampled in Phoenix, AZ, and rural locations in the Southwest and Northeast, in each case applying multiple methods to a common data set. In various combinations, the speciation methods CMB, UNMIX, and PMF of approaches 1 and 2 have been compared with each other and with spatial correlation and trajectory methods representing approaches 3 and 4. A conclusion that emerges clearly and consistently from each of these exercises is that analysts using different methods benefit from interacting with each other and comparing notes. Any single approach leaves some ambiguities unresolved, and a second approach, with its own, but different, ambiguities, can create a sort of stereoscopic vision. Moreover, investigators regularly discovered previously overlooked data issues while searching for the causes of disagreements, highlighting the characterization of data quality as an important issue for the new monitoring networks.

Ambient $PM_{2.5}$ Monitoring

Introduction

Ambient $PM_{2.5}$ monitoring methods and results are not explicitly listed as one of the 10 research topics, but they are implicit in topics 1 through 5. One of the difficulties of ambient monitoring is that the needed measurement locations, sampling frequencies, sample durations, periods of record, and observables differ for different purposes (Chow et al. 2002c; Wilson et al. 2002). The major emphasis on $PM_{2.5}$ monitoring methods and locations has been for determining compliance with the 1997 $PM_{2.5}$ standard (62 Fed. Reg. 38651 [1997]). However, 24-hr duration compliance monitoring of $PM_{2.5}$ mass in urban areas is only partially useful for determining exposure, identifying toxic particle sizes and components, understanding atmospheric phenomena, determining source contributions, and quantifying relationships between ambient concentrations and human health.

State of Understanding in 1997

The $PM_{2.5}$ NAAQS were promulgated in mid-year with specifications for a federal reference method (FRM) to be deployed for determining compliance. Up until this time, the only long-term $PM_{2.5}$ database consisted of the IMPROVE measurements taken since 1988 at national parks and wilderness areas. Some $PM_{2.5}$ measurements were available from special research studies and dichotomous sampler networks in several states. Aside from IMPROVE samples, only small fractions of these samples were characterized for elements, ions, and carbon content.

Beta attenuation and inertial microbalance methods were available for continually measuring PM mass, but continuous methods for chemical components were not prominent. Detailed particle-size distribution and ultrafine measurement methods (McMurry 2000) were available, but instrumentation was not perfected for deployment in long-term networks.

EPA was making plans to deploy a large network of $PM_{2.5}$ FRM filter samplers to determine compliance with the new standards.

For ambient air measurements, NRC (1998) expressed concern that "the monitoring program is moving forward rapidly with too narrow a focus on $PM_{2.5}$ (mass)" and recommended that the monitoring program "be designed to support relevant health-effects, exposure, and atmospheric modeling research efforts." NRC (1998) recommended implementation of continuous mass-monitoring technology to determine variations within and between 24-hr filter samples. It highlighted sampling and analysis discrepancies associated with the carbon component of $PM_{2.5}$. It emphasized the need for interaction among scientific communities and EPA in the planning and execution of monitoring networks.

Research Since 1997

The 1997 $PM_{2.5}$ NAAQS and the 1999 regional haze rule (64 Fed. Reg. 35714 [1999]) stimulated substantial enhancement of long-term monitoring networks, sampling and analysis methods, in situ continuous particle analyzers, specialized field studies, and detailed analysis of existing databases. Progress has been supported by a wide range of sponsors, including EPA, National Oceanic and Atmospheric Administration, Department of Energy, National Science Foundation, Department of Defense, Department of Transportation, state and local agencies, and different industries.

Long-Term Monitoring Networks

EPA, in cooperation with state and local agencies, has established a $PM_{2.5}$ mass FRM compliance monitoring network with more than 1,100 locations, much as it was originally planned.

The number of monitors in the IMPROVE network was nearly doubled to 160 sites to provide nonurban $PM_{2.5}$ mass and chemistry and to evaluate reasonable progress toward natural visibility conditions at national parks and wilderness areas (Chow et al. 2002a; Watson 2002). Fifty-four sites in a Speciation Trends Network were established to quantify $PM_{2.5}$ chemical composition in urban areas, and local and state agencies have enhanced these with additional sites. In addition to week-long measurements of acidic species and deposition, CASTnet also includes several sites with 24-hr average $PM_{2.5}$ mass and speciation.

Eight EPA supersites (Fresno, CA; Los Angeles, CA; St. Louis, MO; Houston, TX; Atlanta, GA; New York, NY; Baltimore, MD; and Pittsburgh, PA) were established to evaluate measurement methods, better understand atmospheric processes, and elucidate relationships between a large variety of observables (for example, size, chemical composition, and co-occurring gases) and specific health outcomes. Most of these sites emphasized continuous monitoring of precursor gases, mass, sulfate, nitrate, carbon, and size distributions by a variety of established and emerging technologies. Sampling and analysis methods for carbon are being tested, and specific organic compounds are being sought within the organic carbon fraction. The EPA supersite program served as a model for other sponsors that operated enhanced PM monitoring in other areas.

EPA increased continuous hourly $PM_{2.5}$ monitoring from 50 sites in 1997 to about 200 sites in 2002. $PM_{2.5}$ networks augment sixth-day sampling at about 250 chemical speciation network sites that include 54 every-third-day chemical speciation sites.

EPA technical working groups were established to evaluate existing air monitoring networks and to formulate a national ambient monitoring strategy (EPA 2003c). This "strategy" (which has been finalized) provides a framework for integrating several existing networks (for example, state and local air monitoring stations [SLAMS], national air monitoring stations [NAMS], $PM_{2.5}$ network [FRM, chemical speciation, IMPROVE, super sites], CASTnet, photochemical assessment measurement stations [PAMS], and air toxics monitoring network) (Demerjian 2000) to address common atmospheric problems (for example, excessive PM, O_3, hazardous air pollutants, and haze). This strategy intends to optimize resources and

balance needs between different network objectives, such as (1) issuing forecasts and alerts, (2) tracking trends, (3) supporting atmospheric and health research, (4) quantifying source contributions and assessing the effectiveness of control efforts, and (5) determining compliance with standards. An important change in approach is to deemphasize the compliance monitoring in favor of a multipurpose national network that will obtain more information for the same cost as current monitoring efforts. It recommends eliminating nearby $PM_{2.5}$ monitors that provide similar information, replacing sporadic filter sampling with continuous monitors, and increasing spatial coverage with less costly monitors (for example, nephelometers and portable filter samplers) to better represent human exposure and to understand contributions from different spatial scales.

This monitoring strategy is the most direct response to NRC's (1998) network recommendations. Its development to date has involved the state and local agencies that operate the networks. Future development needs to involve health and air quality researchers. The strategy needs to explain how well data acquired from 3,000 ambient monitoring sites support exposure assessment, health effects, and atmospheric modeling needs and how a redesigned network would improve the value of information for the same expenditure.

The National Core (NCore) Network would be the centerpiece of this strategy with three levels of monitoring detail. Level 3 sites would have wide spatial coverage for key pollutants of concern (such as O_3, $PM_{2.5}$, PM_{10}), preferably with inexpensive continuous PM monitors that require minimal site preparation, and would sacrifice some measurement accuracy for spatial and temporal coverage. Level 2 sites would consist of multipol lutant or backbone sites and include more detailed and accurate particle size, chemical speciation, and continuous measurements consistent with the technical expertise and budgets of state and local agencies. Level 1 sites would include a few supersite-type platforms in contrasting communities that could be used for serious research on health and atmospheric processes. Level 1 NCore sites would also serve as test sites for new technology, some of which would eventually be used at level 1 and level 2 sites.

The NCore concept is a major change from the past, and it faces opposition. Its success or failure will depend on building flexibility into the compliance program, as FRMs cannot be expected to meet the multiple needs of such monitoring. NCore should also be better coordinated with the available and needed meteorological measurements for modeling past events and forecasting future ones. Major efforts by EPA and NOAA to provide health-related air quality information in an anticipatory fashion would do much to protect public health if the forecasts were accurate.

Monitoring Technology

Much progress has been made in monitoring technology since 1997, especially for continuous and particle size monitors. Research by the supersites teams has shown how recent redesigns of scanning mobility analyzers and optical particle counters can be operated for more than a year with acceptable levels of operator attention and skill. Continuous monitors for sulfate, nitrate, and carbon are also commercially available and reasonably practical to operate for the long term. However, equivalence and comparability between the continuous monitors and filter-based measurements need to be evaluated. Experimental systems for time-resolved elements and ammonium have been demonstrated, although they are not yet practical for long-term networks. A dozen in situ aerosol mass spectrometers have been constructed and applied that measure size and several aspects of chemical composition on a continuous basis. Although standardization methods and operating procedures are still under development, these technologies are applicable to level 1 Ncore sites, and some of them will soon be applicable to level 2 sites.

A plethora of light-scattering particle detectors have become available, many of which are inexpensive and battery operated. A smart heater has been demonstrated for these detectors that heats the incoming air only to a preset humidity, thereby evaporating liquid water in the particles while minimizing evaporation of volatile compounds, such as ammonium nitrate. Battery-operated Minivol filter samplers have been adapted for chemical measurements with impregnated backup filters to acquire nitric acid, NO_2, SO_2, and ammonia. With proper procedures, $PM_{2.5}$ measured by those devices can be approximately equivalent to measurements obtained through the use of the FRM (Baldauf et al. 2001). These simpler technologies could be used for outdoor, indoor, and microenvironmental sampling.

Several speciation filter samplers are commercially available that permit sequential samples, different series of denuders, filters and backup filters, and parallel samples. These samplers provide more accurate quantification of volatile species, gases adsorbed onto filters, and a wider range of chemical characterization. For practical purposes, the FRM sampler is obsolete for all but $PM_{2.5}$ compliance measurements, as it does not have the flexibility of speciation samplers for detailed chemistry, nor does it have the simple logistics and low costs of the Minivol sampler.

Several comparison and characterization studies have been completed for the FRM, and it has been shown to be adequate for its compliance mission. A number of publications examine various properties of the $PM_{2.5}$ FRM sampler (Pitchford et al. 1997; Tropp et al. 1998; 63 Fed. Reg. 18911

[1998]; 63 Fed. Reg. 31991 [1998]; Musick 1999; Kenny et al. 2000; Tanner and Parkhurst 2000; Chung et al. 2001; Noble et al. 2001; T.M. Peters et al. 2001a,b,c,d; Vanderpool et al. 2001; Eisner and Wiener 2002; Pang et al. 2002a,b; Poor et al. 2002; Watson and Chow 2002b; Chow et al. in press). A sharp-cut cyclone has achieved equivalence status and is replacing the WINS-96 impactor in many FRMs. The cyclone has a larger capacity and uses no oil on the impaction surfaces, thereby saving substantial maintenance costs. As with all filter samples, the $PM_{2.5}$ FRM sampler suffers from changes in the state of the aerosol after sampling, owing to changes in equilibrium over the 24-hr sampling period. Gas adsorption and particle volatilization can also occur during passive periods before and after sampling. Comparison of a new technology with the $PM_{2.5}$ mass FRM sampler is not a good way to evaluate the validity of the newer technology, although it is useful to establish equivalence, comparability, and predictability for different aerosol compositions and sampling environments.

One of the challenges in integrating different networks is to ensure consistency in sampling and analysis protocols. For example, an attempt was made to integrate data from the $PM_{2.5}$ Speciation Trends Network (STN) (operated by EPA) with data from the IMPROVE network (operated by the National Park Service, Federal Land Managers, and EPA) for air quality assessment, modeling, and health studies. Discrepancies between the two $PM_{2.5}$ networks were found in sample archiving (only retained for 6 months in the STN versus permanently archived in the IMPROVE network), blank subtraction (applied in the IMPROVE network but not in the STN), carbon analysis (STN protocol of the thermal and optical transmission method for organic and elemental carbon without fractions versus IMPROVE protocol of the thermal and optical reflectance method for eight fractions of organic and elemental carbon), and uncertainty propagation (reported only in the IMPROVE network). Different methods applied in these two networks can result, for example, in a factor of two differences in elemental carbon concentrations (Chow et al. 2001). These differences create large uncertainties in $PM_{2.5}$ source apportionment, regional haze assessment, and global climate-change modeling.

Special Monitoring Studies

Several integrated studies have been initiated since 1997 that will provide databases useful for air quality modeling and health studies. These were designed for specific objectives, but the databases they acquire may be useful for other objectives:

- Central California $PM_{10}/PM_{2.5}$ Air Quality Study (CRPAQS): This major field study from December 1999 through January 2001 acquired $PM_{2.5}$ measurements at more than 100 locations throughout central California using a three-level network similar to that of NCore. Many measurements from the Fresno supersite were duplicated at a nonurban site approximately 100 kilometers (km) south to contrast the regional with urban characteristics. Detailed organic compounds and precursor gases were quantified during wintertime episodes. Upper-air meteorological measurements were acquired with sodars (sonic detection and ranging), radar profilers, and rawinsondes to complement about 400 surface meteorological sites. Data validation, data management, data analysis, and modeling efforts are in progress (Watson et al. 1998b).
- FACES: The Fresno Asthmatic Children's Environment Study is designed to examine the acute and chronic health effects of air pollution on children with asthma who reside in the Fresno and Clovis area between November 2000 and December 2004. Exposure assessment includes the centrally located Fresno supersite ambient monitors as well as neighborhood, home, and some personal monitors. The detailed exposure monitoring will allow FACES to evaluate which components of air pollution, in combination with biological agents, influence the natural history of asthma. The detailed descriptive data collected as part of the health assessments will allow FACES to identify biological and environmental characteristics that make some children more susceptible to the health effects of air pollution (Tager et al. 2002).
- MARCH: The Maryland Aerosol Research and Characterization Study is a multiyear field study focusing on both short-term (episodic) and long-term (interannual) variations of $PM_{2.5}$ chemical composition in an urban area of the U.S. Mid-Atlantic region. Data was acquired at Fort Meade, Maryland, in 10 seasonally representative months over 4 years (1999-2002). Measured parameters included precursor gases (ammonia [NH_3] and nitric acid [HNO_3]) and pollution tracers (CO, SO_2, O_3, $NO/NO_x/NO_y$, and VOCs) besides aerosol mass and chemistry. Upper-air meteorology was measured using a radar profiler. Solar insolation, temperature, relative humidity, pressure, and surface wind speed and direction were monitored throughout the entire period. Additional measurements included airborne measurements of trace gases and atmospheric absorption during approximately 20 pollution episodes (Chen et al. 2001, 2002).

BRAVO: The Big Bend Regional Aerosol and Visibility Observational Study, conducted between July and October 1999, was designed to determine the long-range, transboundary transport of visibility-reducing

particles from regional sources in the United States and Mexico and to quantify the contributions of specific U.S. and Mexican source regions and source types responsible for poor visibility at Big Bend National Park (Green et al. 2000).

SEARCH/ARIES: The collaboratively funded joint Southeastern Aerosol Research and Characterization (SEARCH) study (Hansen et al. 2003) and the Aerosol Research and Inhalation Epidemiology Study (ARIES) (Van Loy et al., 2000) were designed to produce a comprehensive air quality climatology for the southeastern United States and to study the associations between health outcomes and specific components of PM as well as copollutants and meteorological variables, respectively. ARIES uses an augmented SEARCH monitoring station in Atlanta to collect its core air quality data. SEARCH began collecting data at eight sites in the southeastern United States in August 1998 and will continue through 2005. ARIES started at the same time and will continue through the end of 2003. Twenty-four integrated samples of $PM_{2.5}$ mass, sulfate, nitrate, ammonium, metals, organic carbon, black carbon, and $PM_{10-2.5}$ mass, sulfate, nitrate, ammonium, and metals and continuous measurements of meteorological parameters, SO_2, NO, NO_2, NO_y, CO, O_3, $PM_{2.5}$ mass, sulfate, nitrate, and ammonium are made at all SEARCH sites. Data are available at ARA (2003). In addition, PM acidity, ammonia, speciated VOCs, speciated semivolatile organic compounds, pollen spores, water-soluble metals, and size-fractioned ultrafine particles have been measured at the ARIES core site.

What Has Been Learned?

Hundreds of articles have been published since 1997 about new measurement methods and characterization of well-established methods. Of particular note are several books and reviews that summarize and criticize the literature (Lodge 1989; Kerker 1997; Chow and Watson 1998; Flagan 1998; Spurny 1998, 1999; Watson et al. 1998a; Knutson 1999; Landsberger and Creatchman 1999; Lane 1999; Demerjian 2000; Jacobson et al. 2000; McMurry 2000; ACGIH 2001; Baltensperger 2001; Baron and Willeke 2001; Brimblecombe 2001; Chow et al. 2001, 2002a,b,c; McMurry and Sakurai 2001; Schmid et al. 2001; Currie et al. 2002; Murphy and Morrison 2002; Watson 2002; Wilson et al. 2002; Fehsenfeld et al. 2003). These publications are most useful for obtaining an overview of progress, even though each reviewer has a particular point of view and the reports are

not always consistent with one another. Special journal issues also have been organized to report on the characterization, performance, and comparability of new measurement methods used within the supersite program. In particular, a special issue of *Aerosol Science and Technology* is in press and will feature approximately 20 articles devoted to findings from the supersite program. In addition, other publications and special journal issues on supersite results are forthcoming. Finally, supersite investigators also joined forces to update old and create new procedures for a badly needed revision of *Methods of Air Sampling and Analysis* (Lodge 1989).

Major research results include the following:

- The federal reference method (FRM) equipment and procedures for $PM_{2.5}$, although more sensitive and precise than previous FRM methods used for total suspended particles (TSP) and PM_{10}, are still influenced by particle volatilization and gas adsorption (Pang et al. 2002b).
- Three types of ultrafine particle events have been detected at supersites from long-term monitoring of detailed size distributions: (1) fresh vehicle exhaust, (2) fresh plume touchdown, and (3) spontaneous condensation in relatively clean air. The final mechanism may be a neighborhood-scale or urban-scale source of ultrafine particles that is not indicated by high $PM_{2.5}$ mass concentrations (Woo et al. 2001).
- Short-duration (5 min to 1 hr) measurements of $PM_{2.5}$ mass, black carbon, sulfate, nitrate, and heavy metals show pulses of increased concentration as well as diurnal cycles. These pulses and cycles are not evident in 24-hr average samples and might have health consequences that are masked by longer averaging times (Watson and Chow 2002a).
- SO_2 reductions in the eastern United States might not result in changes in $PM_{2.5}$ that are equal to decreases in sulfate concentrations, because ammonia is freed for combination with available nitric acid (Ansari and Pandis 1998; West et al. 1999) to form ammonium nitrate that replaces some of the sulfate in $PM_{2.5}$.
- The increment in urban-scale and neighborhood-scale $PM_{2.5}$ is mostly due to fugitive dust and carbon when compared with the regional-scale composition that is dominated by secondary ammonium sulfate and ammonium nitrate (EPA 2002c).
- "Natural" contributions from wildfires and dust are frequent and sometimes dominant contributors to regional $PM_{2.5}$ and haze in the western United States. Asian and African dust contributions can measurably affect regional $PM_{2.5}$ loading (VanCuren and Cahill 2002).

What Remains To Be Done?

EPA's ultimate goal must be to have integrated, flexible, and well-tested particle models available for distribution and use for development of PM management strategies. It is still not clear that EPA is making the appropriate commitment to have the best models available for use at the local air quality management levels. In addition to the very limited progress on emissions characterization, the committee has substantial concerns about the air quality management community's access to fully operational source and receptor modeling tools for the NAAQS implementation tasks it will need to undertake in the coming years.

From the presentations made at the Source-Receptor Modeling Workshop held at EPA in March 2002, it was clear that a variety of modules and techniques to improve the EPA-developed Models-3 are still under development. Moreover, given the continuing improvement in the theoretical understanding of the processes within the atmosphere that relate to the chemically and size-resolved particle concentrations, the model may never be considered complete. Instead, there will be a continuing need for improvement in Models-3. Comprehensive emission inventories also appear to be lacking for the model, especially for ammonia and organic carbon.

At present, EPA projects are developing methods to treat the oxidation of VOCs and production of condensable products and the thermodynamics of semivolatile organics. They are examining new methods for treating emissions of sea salt, dust, and biomass-burning emissions, and they are running models for entire year scenarios (which could yield information on how well the model treats the rate and frequency of SO_2 conversion to sulfate and NO_x conversion to nitrate and which could be used to evaluate simpler, faster models and methods to determine annual PM concentrations from episodic simulations). In addition, development is planned for more detailed particle representations (sectional models and models to treat externally-mixed particles). As EPA moves into the next phase of PM control strategies, it will be important to develop test scenarios for Models-3 that allow adequate testing of its representation of the suite of processes.

Efforts are under way to link and integrate air quality models with exposure and dose models. However, a major problem with this effort is that CMAQ and similar models only provide results at the resolution of a 4 km × 4 km grid cell size. Exposure often occurs at a sub-grid cell scale and in cities where there are street canyons, substantial local traffic sources, and other highly complex phenomena that cannot be reproduced in the current models. Thus, additional work is needed to explore this smaller

scale modeling problem and to provide appropriate data to be able to test the air quality and any interrelated exposure and dose model.

Although the instruments needed to monitor air quality are largely in place, much remains to be done if the data they produce are to be used effectively. There are major sampling and analytical uncertainties in the measurement of major particle species, for example, most critically organic material. EPA has yet to adequately address discrepancies between its STN and IMPROVE networks, which involve analytical methods, blank correction, and the propagation and reporting of uncertainty. More generally and more fundamentally, EPA has yet to articulate a plan for continuing comparisons that systematically test its emission data, source and receptor models, and ambient data against each other.

EPA's (2001) attainment-demonstration guidance recognizes the uncertainties inherent in any air quality simulation efforts. It emphasizes a weight-of-evidence approach rather than an application of a single model to understand source-receptor relationships. It also emphasizes the complementary application of both source and receptor models to develop a conceptual model that can guide decisionmaking. Those ideas are further developed by NARSTO (2003), which contains numerous specific recommendations that EPA and other sponsoring agencies should consider when planning further modeling efforts.

Simpler, more user-friendly software is also needed to explore and understand such concepts as (1) which subregions contribute emissions most often and which contain the highest emissions; (2) how quickly do precursor pollutants turn into particles when injected into polluted and unpolluted environments; (3) where and when do different precursors limit or enhance particle formation; (4) how much faster would pollutants be removed in the gas phase rather than the particle phase; and (5) what are the multiple effects of NO_x and VOC emissions on O_3, sulfate, nitrate, and secondary organic aerosol. Exploration of these questions would help decision-makers decide what is knowable and what can be better known with a modest investment.

EPA must now provide the leadership for a coordinated effort to compare various models and their implementations and to incorporate refinements developed in academic and other research institutions to improve those models earmarked for regulatory applications. EPA will be required to increase the level of attention it is now giving to characterizing emissions and to develop the large-scale, three-dimensional field studies that are necessary for rigorous evaluation of source-oriented models. Although EPA might not have large resources for model evaluation, it can participate in and help to shape efforts involving other government agencies

and private institutions with substantial field programs, enhancing such efforts in ways that disproportionately increase the value of the resulting data for EPA's own applications.

The final adequacy of air quality models used to protect community health will have to be evaluated within the evolving context provided by an understanding of which features of particle exposures are most relevant to health risks. At the same time, interpretations of health findings will have to reflect an understanding of source-ambient relationships in the atmosphere. Therefore, information must continue to flow between health-effects and atmospheric scientists.

RESEARCH TOPIC 5
ASSESS HAZARDOUS PARTICULATE MATTER COMPONENTS

What is the role of physicochemical characteristics of particulate matter in eliciting adverse health effects?

Introduction

Ambient PM is a complex mixture of particles having different sizes and different chemical compositions. Indeed, even one individual particle may contain several chemical entities. For example, a core particle having one chemical composition can have other chemical entities adsorbed onto its surface, thus, essentially yielding a particulate chemical mix.

The basic goal of this research topic is to improve the understanding of the role that specific physicochemical properties of ambient PM may play in eliciting adverse health effects. The consistency of findings of epidemiological studies across diverse geographic regions, where substantial variation occurs in such characteristics, suggests that risk might depend only on the level of exposure. On the other hand, relative risk estimates related to exposure do vary somewhat in different regions of the country, suggesting that toxicity might be modulated by specific properties of PM within the various areas being studied. In addition, the issue of appropriate exposure-dose metrics for use in evaluating health effects is also included in this research area.

The specific research recommendations prepared by this committee are as follows:

- Assess relevant dose metrics for PM to relate to adverse health outcomes. That would allow for determination of whether there are better measures of exposure or dose than simply mass concentration, the metric used in almost all epidemiological and toxicological studies.
- Evaluate the role of particle size (for example, ultrafine [less than 0.1 μm] versus fine [2.5 μm] versus coarse [between 2.5 and 10 μm]) in health outcomes related to PM. Ambient PM consists of particles within a wide size range, and it is important to understand the relationship between size and toxicity. This assessment is complicated by the association between chemical composition and size in many locations, and appropriate exposure metric and size might also be related.
- Determine the role of PM chemistry in PM-related health outcomes. This research area is aimed at determining whether the toxicity of PM is nonspecific (that is, whether biological responses to exposure are merely due to deposition of the particles per se) or whether it depends on the specific chemical composition of the exposure atmosphere.

Over the years, there has been considerable evolution in understanding the potential health effects and ultimate toxicity of particles of various sizes and chemical compositions.. The first PM air quality standards (NAAQS) were based on measures of total suspended particulates (TSP), a mass-based measure of the sum total of all particles that were collected on a filter over a specific sampling period. Several early epidemiological studies found associations between TSP concentrations, as well as with several other nonspecific PM measures, such as British black smoke and coefficient of haze, and risks for adverse health outcomes. Subsequent refinements in the understanding of airway dosimetric patterns led to a revision of the PM NAAQS, PM_{10} replacing TSP as the indicator. PM_{10} is essentially a mass-based measure only of those particles less than 10 μm in diameter. Numerous epidemiological studies found health effects associated with this measure as well. Differences in depositional patterns between smaller particles (less than 2.5 μm) and larger particles (larger than 2.5 μm) and the recognition that the smaller and larger particles were generally associated with different sources and generation processes—thus, probably having different chemical makeup—led to the development of a $PM_{2.5}$ size standard. At the time, there was little epidemiological information to support this change, largely because monitoring data for $PM_{2.5}$ was available from only a small number of research settings. The available evidence was derived principally from the Harvard six-cities studies (Schwartz et al. 1996; Dockery et al. 1993). However, even within the $PM_{2.5}$ mode, toxicological findings have suggested that the smaller particles (that is, those less than 0.1 μm in diame-

ter) might be of special health concern, and these particles should be considered in an epidemiological context.

State of Understanding in 1997

As noted in the committee's first report, there was "insufficient understanding of the relationships between chemical composition, shape and size of ambient particles and resulting health effects" (NRC 1998). There was substantial epidemiological literature relating health effects to measures of PM, but only a very few studies incorporated specific PM characteristics or components. A few studies suggested that $PM_{2.5}$ was a better measure of response than PM_{10}, but this issue could not be resolved definitively from epidemiological studies because of the limited $PM_{2.5}$ data. Some consistency across studies performed in different areas provided the basis for the hypothesis that health responses were related to the mass of particles common to many areas of the country rather than to specific components in the air pollution mixture that can vary from area to area. However, inconsistencies in methodological approaches across studies generally made it difficult, if not impossible, to compare results across studies. In addition, the results across epidemiological studies were not always consistent. Some toxicological evidence showed that there could indeed be differences in the toxicity of different PM components.

In the epidemiological context, the efforts mentioned above clearly required accompanying monitoring efforts. Before 1997, data on alternative particle size measures and chemical speciation were limited to a very few research sites. Data on alternative size fractions of PM were not monitored in the United States. The Harvard six cities study collected data on measures of both coarse and fine fractions of PM_{10}, as well as some elemental data obtained with X-ray fluorescence spectrometry (XRF) analyses.

With respect to chemical composition, most epidemiological and toxicological studies conducted before to 1997 were largely focused on only one component of PM, namely, secondary inorganic particles and, within this class, inorganic sulfates and acidic compounds. Sulfates were measured in several epidemiological studies as early as the 1970s, but no definitive conclusion was reached about their toxicity per se. One of the problems concerning these compounds is that they are among the largest components of PM, and measures of sulfates are often correlated with concentration of total PM. Correlations with other components have not been characterized; hence, it is unclear whether in these early studies sulfates merely served as a surrogate for fine PM. Acidity was measured

in a small number of epidemiological studies (for example, Klemm and Mason 2000; Lipfert et al. 2000a; Lippmann et al. 2000; Tolbert et al. 2000b; Ito 2003; Metzger et al. 2004). Results have been mixed, and there is no consensus about toxicity in relationship to ambient exposure. Information derived from epidemiological studies about the toxicity of other chemical species was small. However, toxicological considerations raised the possibility that other specific chemical species are of some concern, such as transition metals, organic chemicals, and bioaerosols; however, for the most part, toxicological assessments concentrated on inorganic sulfates, and particle size modes used in such studies were generally in the fine mode range.

What Has Been Learned?

Of the projects that included toxicological aspects of this research topic and began during or after 1997, about three human clinical studies have been completed, five in vitro studies have been completed, and seven animal in vivo studies have been completed. Of the studies initiated during or after 1997, about 10 human clinical studies are still in progress, over 20 in vitro toxicology studies are still in progress, and over 40 animal in vivo studies are still in progress, according to the Health Effects Institute database.

With respect to epidemiology**,** it is difficult to specify a specific number of studies on this topic. First of all, research funding by category is available only for a subset of funding agencies. Second research in this area is often combined with other research areas (for example, topic 7, combined effects of PM and gases). If a study had information on PM components, it probably had information on gaseous pollutants as well. Most of the studies in this area have focused on a small number of components of PM and sometimes only on one, such as the "coarse fraction"; in other cases, an alternative measure of PM (such as black smoke) was studied. Because such measures are different from the $PM_{2.5}$ measure, studies that have considered one or more components are included in this category.

For toxicological aspects of this topic, a literature database of publications provided by EPA identified almost 200 peer-reviewed papers published between 1997 and 2002 that addressed this topic. Of these papers, about 50% described studies conducted in vitro, 40% described studies conducted in animals, and less than 10% were controlled clinical studies in humans. A few papers described studies that involved both in vitro and in

vivo exposures. Of the in vivo studies, including those conducted in humans, about two-thirds used instillation as the mode of delivery and only one-third used inhalation. The problem is that, in most cases, instillation involved use of very high exposure or dose concentrations of particulates; furthermore, it is difficult, if not impossible, to relate exposure concentrations used in in vitro studies to in vivo conditions. Thus, although both instillation and in vitro studies often claim to be examining mechanisms, it is quite possible that the mechanism that occurs at such high concentrations is not the same as that occurring at more realistic exposure concentrations.

Dose Metric

Before 1997 and even continuing to this day, the most common metric used to relate exposure concentration to biological response is size-specific mass concentration of PM in the exposure atmosphere. However, only a few studies since 1997 have addressed the issue of particle surface area in the context of size and particle number concentration as alternative dose metrics that might explain health effects following exposure.

Studies that have examined alternative dose metrics are largely toxicological studies. For example, recent studies indicated that particle surface area, especially for ultrafine particles, might play a part in adverse effects, such as induction of pulmonary inflammation, and in some cases, might be more related to response than the traditional mass concentration measurement or specific particle size. Surface area might have some role in toxicity, because aerosols consisting of particles having low intrinsic toxicity but having large surface areas appear to induce greater inflammatory response than do particles having greater toxicity but smaller surface-area characteristics (Oberdorster et al. 1992; Li et al. 1999).

However, the number of such studies is still small, and additional work on other potential dose metrics, such as particle number, is needed, because response might be a function of a number of such metrics. For example, one study noted that the surface charge (zeta potential) on PM was a good predictor of response (Veronesi et al. 2002). Furthermore, the specific dose metric that best relates to response may differ for different particle size ranges within the ambient aerosol.

Particle Size

Before 1997, epidemiological and toxicological studies focused on

PM_{10}, which included ultrafine, fine, and coarse particles. More recently, some attempts have been made to size-fractionate exposure atmospheres to evaluate specific responses to the fractions. However, the number of studies that directly compare toxicity of different size fractions of PM is still small. In those few direct comparisons performed since 1997, ultrafine particle exposure seemed to result consistently in greater pulmonary response than did the same mass dose of fine particles having the same chemical composition (for example, Oberdörster et al. 2000; Donaldson et al. 2001). Thus, it is possible that for one specific size class, namely, the ultrafines, both size and chemistry determine response; for other size modes, chemical composition might be a better determinant.

Thus, there is clearly a need for additional studies that specifically examine the relationship between particle size and response. Furthermore, there are major uncertainties even related to size. For example, some studies using ultrafine particles indicate that it is specific chemical makeup rather than particle size that is the predictor of biological response. Ambient air coarse particles also had a greater toxic effect than fine particles had in some model systems (R. Devline, EPA, pers. Com., 2004). However, size and chemistry of ambient particles are interrelated, and certain chemicals are associated with certain size fractions. Thus, to determine the role of size versus chemistry, laboratory-generated aerosols must be used that have the same chemical composition but are in different size ranges. This experimental approach has rarely been followed.

In terms of evaluating particle-size effects in epidemiological studies shortly before and after 1997, simultaneous measurements of $PM_{2.5}$ and the coarse fraction of PM_{10} became available at several locations (Burnett et al. 2000; Burnett and Goldberg 2003; Goldberg and Burnett 2003; Mar et al. 2003). These data have allowed greater comparison of those two size fractions, and such data are expected to increase substantially in the near future. Results to date suggest that the coarse fraction of PM_{10}, as well as the fine fraction ($PM_{2.5}$), can be associated with health responses. It is expected that many additional analyses of these size fractions will be available shortly as monitoring data become more widely available. It is hoped that these additional analyses will provide sufficient data to reach some definitive conclusions about the importance of the coarse fraction relative to the fine fraction.

Data for other size fractions are not routinely collected and are available only for specific studies. For example, only three studies have reported results that relate health outcomes to the ultrafine fraction of PM: one study in Erfurt, Germany (Peters et al. 1997; Wichmann et al. 2002), one in Atlanta (Tolbert et al. 2000a), and one in the United Kingdom (Osunsanya

et al. 2001). The results from these studies have both positive and negative findings. Given the small number of sites where ultrafine measurements are being performed, only limited additional evidence can be anticipated over the short term. The study conducted by Tolbert et al. (2000a) in Atlanta appears to be the only published epidemiological research that considered the surface area of ultrafine particles. There is also a question about the degree of association between measures of ultrafine particles from central monitoring stations and from individual exposures. An understanding must be reached about how to characterize the exposures to ultrafine particles, and studies must be undertaken in conjunction with coordinated monitoring programs that reflect that knowledge. Systematic efforts to compare other measures of particle size are even more limited. Such efforts will be important, because measures of the various components of PM are often correlated, and it will be important to understand the extent to which some measures serve as surrogates for others.

Chemical-Specific Effects

Since 1997, toxicological studies have extensively evaluated particle chemistry as a determinant of biological response. However, the specific chemical components have generally been the same as those examined in previous years.

The role of metals, especially transition metals, in eliciting biological responses has been extensively evaluated. A large number of studies using various materials have concluded that these metals, especially those that are water soluble, can have a role in effects observed following inhalation of ambient PM (Frampton et al. 1999; Campen et al. 2002). Some of the metals that have been more extensively examined are iron (Fe), vanadium (V), and nickel (Ni). These have been associated with various effects, including production of reactive oxygen species, pulmonary inflammation, enhanced sensitization to antigens, and increased susceptibility to respiratory tract infection. There has also been some indication that they, either alone or in combination, have some role in cardiac effects related to PM.

Although most recent toxicological studies have involved evaluation of metals, only a few have evaluated other chemical components of ambient PM in terms of their potential to induce toxicity following exposure. Fewer studies have evaluated organic components of the aerosol, and these have shown effects, mainly induction of reactive oxygen species, that appear to be related to these constituents (Li et al. 2002). A greater number of studies have evaluated diesel exhaust particles in terms of their ability to result in

pulmonary sensitization. Water-soluble components of diesel exhaust particles appear to be more effective in inducing toxicity—in this case, cardiac effects.

Thus, if some generalization can be made based on the more recent data from toxicological studies, solubility in tissue fluids might be a factor in determining toxicity of some particle-associated chemicals. However, the evidence is still mixed. Some studies have shown that the insoluble fraction also may have some biological activity as well, and in one study, the insoluble constituents of PM resulted in effects. Thus, the increased number of studies has provided a larger database, but one that still has not been able to answer the research question posed in a definitive manner. The issues of interest have shifted, however. Before 1997, inorganic sulfates were considered to have a major role in effects of ambient PM; now more research is aimed at examining effects of metals in that regard. Furthermore, little work has been reported on potential effects of biologically derived aerosols. As a further complication, it is difficult to separate out specific characteristics of particles in terms of their role in toxicity. For example, some studies suggest that the surface chemistry of particles may be more important than specific size—that is, similar-sized particles having different surface chemistry had different toxicity (Blackford et al. 1997).

As alluded to above, to separate out effects of different characteristics of ambient PM in terms of their contribution to toxicity, it is necessary to develop well-defined "model" particles that will allow control of specific characteristics. Before 1997, such surrogates have included residual oil fly ash (ROFA), acidic sulfates, and black carbon. These particle types are still being used in more recent studies. The instillation mode of administration is also commonly used. However, in a number of cases, when instillation and inhalation were both used in the same study, different responses were produced. Thus, it is critical that exposures be performed using the most realistic mode of exposure, namely, inhalation at relatively low exposure concentrations to avoid problems in interpreting results due to chemistry as opposed to mode of exposure and subsequent delivered dose.

In epidemiological attempts to relate health effects to specific chemicals, results tied to chemical components of PM have been few because, as noted, the air quality monitoring of these components has been limited. EPA set up a network of supersites where much more detailed characterization of air quality was undertaken. However, in general, these sites were set up and measurements made with insufficient consideration of accompanying epidemiological studies. Hence, the number of studies using these data is small, and no results have been published using any data from the EPA supersites. However, a small number of epidemiological studies using data

from supersites is under way, and results will presumably become available in the next few years.

As part of its monitoring program, EPA set up a number of speciation sites where more measures will be available of PM components, specifically, sulfates, nitrates, elements (derived from XRF measures), and organic and elemental carbon. As these data become available, they will provide an important source for additional analyses. Of concern, however, is whether these measures are sufficient. The metal data, for example, are for total metals, and it is not known whether this is the optimal metric for potential impacts on health. As noted, some toxicological studies have suggested that soluble metals might be a better measure; furthermore, there has been some discussion about the medium used to define solubility. The valence states of some metallic species have also been considered to be possibly relevant to toxicity. Also, organic carbon and elemental carbon are mixtures, and it is unclear whether these mixtures are relatively consistent over time and space. Additional research results from the atmospheric chemistry community would aid in this regard.

There are several epidemiological studies since 1997 that made use of available monitoring data (Mar et al. 2000). Several studies have continued to examine sulfates and acidity. The results from these studies have been mixed, and when only a few components of PM are considered in an analysis, it is not clear whether the results of that analysis are appropriate for the fraction studied or for other fractions that might be correlated with the measured fraction (that is, the surrogate issue). An additional group of studies have examined measures of carbonaceous matter, such as black smoke (a commonly reported measure in Europe), black carbon, elemental carbon, and organic carbon (Tiittanen et al. 1999). Precise chemical definitions of these are not generally available; hence, it is not clear whether these measures are indicators of the same mix of chemical species across studies and study locations. It will be particularly important to characterize these measures chemically to gauge their consistency in producing responses.

A few epidemiological studies made use of metal measurements, usually obtained from XRF analyses. These studies are of two types: those that examine the association between health impacts and specific metal species directly and those that derive an air quality index (often associated with source) using metal concentration data and relating this index to health outcomes (Magari et al. 2002). Studies using the first approach have generally not yielded consistent results. Caution needs to be used in interpreting these results, because, as noted, the correct metal metric might not have been considered. The second approach can yield results indicating particular sources as having an adverse effect on health. The methods used to

derive indices must be carefully examined, and this method cannot indicate those specific pollutants from a given source that might be important. However, differences in the indices and methods used make it difficult to compare these studies. Nevertheless, these studies have found that associations between health measures and indices vary by index.

There have been additional substances examined (for example, polar VOCs, benzene, endotoxins, and bioaerosols) in a few epidemiological studies, but their examination has been limited to isolated studies. These studies have all suggested that these substances can affect toxicity; however, results are too limited to reach any overall conclusions.

A number of studies have examined several components of PM and air pollution in the context of a specific study (for example, Mar et al. 2000; Tolbert et al. 2000a,b; A. Peters et al. 2001a). These studies have the advantage of applying a consistent methodology to examine several components of air pollution and PM with the same health data. Such analyses can more easily indicate the relative importance of the various fractions of air pollution and indicate those that are more or less toxic. More studies that provide a consistent approach to examining several components of PM and air pollution are clearly needed. In those studies that have applied a consistent and balanced approach to examine several components of PM, differences have been found in the associations between the various components and health measures. The results support the hypothesis that different chemical components of the PM mixture exhibit different toxicities.

Synthesis

In spite of important differences in exposure mode and concentration, specific characteristics may be involved in adverse health effects from ambient PM in toxicological and epidemiological studies. For example, acid aerosols seem to have toxicological effects only at relatively high exposure concentrations in toxicology studies, and they do not seem to have consistent effects from results of epidemiological studies. One instance in which there is good coherence and convergence between epidemiological and toxicological studies involved work in the Utah Valley (Pope et al. 2002). Epidemiological studies were carried out under two conditions. In one, there were significant metal particles as part of the ambient PM and, in another, metal levels were significantly reduced. Toxicological studies were subsequently carried out using particles and extracts obtained from filters during these two time periods. According to results obtained through both

disciplines, the period of high metal content was associated with greater effects.

Scientific Value

Rather than adding to the number of potential characteristics of ambient PM associated with health effects, toxicological work performed since 1997 has shifted in thinking. Today, inorganic secondary particles, such as sulfates, are not considered as likely to be important as soluble transition metals, which are receiving more attention. There is also increasing evidence that specific size ranges of particles, especially ultrafine, may have to be considered in terms of selective toxicity.

An important bridge between epidemiological and toxicological evidence is the evidence of effects seen in animals exposed to "real-world" particles on site, such as near a highway or in an urban area, compared with those seen in animals exposed to air in cleaner areas (Calderón-Garcidueñas et al. 2001a,b). These studies can provide insight in relating the effects in humans to those in animals similarly exposed. These studies indicate that health effects in the animals are associated with PM having certain chemical characteristics. For epidemiology, the research results in this area have been limited to date, with commensurate scientific value. The results suggest, however, that different fractions of PM exhibit different toxicities; hence, this issue merits further examination.

Decisionmaking Value

A large proportion of the toxicological studies use instillation of particles, while others use in vitro exposure techniques. In both cases, the doses are usually high, and in the latter, they generally cannot be related to in vivo exposures, as noted earlier. Thus, there is still a paucity of studies using realistic concentrations of particulate exposure. Most studies cannot discriminate between the effect of particle size and that of chemical properties, because the two are not independent variables. Nonetheless, there does appear to be a shift in thinking about specific particle characteristics that are probably involved in health effects from exposure to ambient PM. However, the committee did not identify any new data or any data anticipated over the short term that would be likely to affect the indicator used in the PM NAAQS.

In terms of epidemiological research, results to date are unlikely to influence the current standard setting except possibly for those results for the coarse fraction of PM_{10} ($PM_{10-2.5}$). Results to date accompanied by additional results could, however, provide greater information about those fractions of PM and air pollution that can most impact health. Future state implementation plans (SIPs), which are plans for reducing emissions so that an area can come into compliance with air quality standards, could therefore benefit from new and existing research in this area. Such information would enable SIPs to focus emission-control efforts on sources contributing the greatest potential health impacts.

Information Expected in the Near Future

In epidemiology, the availability of data from supersites and speciation monitors will allow additional analyses of PM components from various regions of the country. There is some concern, however, that the total metal species measured at speciation sites might not be the best measure of bioavailable metal. In toxicology, work is likely to continue on those specific physicochemical properties that have been shown to relate to adverse health outcomes.

What Remains To Be Done?

Progress in the area of topic 5 since the committee's first report in 1998 has consisted of an increased number of studies examining a greater number of particulate chemical and size characteristics than previously performed. The results of these studies have not demonstrated any consistency that can narrow the array of particle characteristics that modulate the toxicity of ambient PM. These efforts have not provided much insight into how specific PM characteristics might modify interactions between PM and other pollutants.

Few conclusions regarding the health significance of particle characteristics have resulted from epidemiological research, because monitoring data have provided little information on these characteristics. The small number of published epidemiological studies that have examined several particle characteristics do not yet allow an overall inference about the characteristics that are most important. The studies do indicate, however, that some characteristics, such as carbon content, warrant further investigation (for example, Tolbert et al. 2000a; Mar et al. 2003; Metzger et al.

2004). Toxicological and epidemiological studies should be better integrated so that information generated by toxicologists could be assessed to the extent possible by epidemiologists. Such integrations will help to determine the relevance of high-exposure studies to effects at realistic concentrations. Furthermore, insights from toxicological studies can reduce some of the uncertainties in interpreting observational studies.

The committee's review concludes that despite the increased research effort, the uncertainties related to topic 5 generally remain comparable to those described in the committee's first report. The studies conducted over the past 6 years indicate the difficulty of the scientific questions and the need for new research approaches, whether toxicological or epidemiological. Advances have not been made that could inform the setting of a NAAQS for PM incorporating refinements related to the physicochemical characteristics of PM. Perhaps a more systematic approach, in which relevance of dose and exposure material is considered, will help to provide advances that will allow decisions to be made on whether PM characteristics should influence the PM standard.

A strategy is needed to ensure that toxicological and epidemiological research is directed toward a greater range of particle characteristics than studied to date. Such a strategy could incorporate both the application of uniform protocols to multiple characteristics and the use of a wider range of investigator-initiated approaches. The goal would be to ensure that no potentially important characteristic is overlooked and that the totality of potential health outcomes is considered for each characteristic. Differences in the spatial homogeneity and measurement error associated with different components of PM need to be addressed in the design and analysis of epidemiological studies to ensure that all components are appropriately considered. Finally, the health significance of specific particle characteristics must be considered in relation to their modulating effects on interactions with other particles or nonparticulate pollutants.

To date, toxicological studies of PM characteristics have been largely designed to determine whether a single physical (for example, PM size) or chemical (for example, soluble transition metal) characteristic could be linked to adverse health responses. Future work needs to extend these investigations in four key dimensions: (1) addressing additional characteristics that have received little attention; (2) defining exposure-dose-response relationships at realistic exposures; (3) making direct comparisons between PM with different studies using identical protocols; and (4) evaluating the importance and role of the characteristic in question as it exists as a component of realistically complex exposures.

Work to date predicated on the hypotheses of individual investigators

has addressed several but certainly not all of the physicochemical characteristics. For example, work on ultrafine PM has focused almost entirely on solid particles, despite much of the ultrafine PM population's consisting of nonsolid condensed organic matter (Sakurai et al. 2003). Similarly, a huge effort has been directed toward the oxidative-driven inflammatory and cytotoxic responses to water-soluble transition metals (Donaldson et al. 1997; Ghio et al. 2000a), but very little effort has been directed toward the inflammatory and cytotoxic effects of PM-bound organic compounds, despite the evidence that this fraction can also operate through oxidative reactions (Li et al. 2002; Yu et al 2002; Reed et al. 2003).

Only a few attempts have been made to directly compare responses and dose-response relationships for different types of particles. Although different protocols would understandably be used to explore effects and mechanisms for different PM characteristics and initial explorations could begin at high doses, an understanding of the relative importance of the PM characteristics also requires head-to-head comparisons of the exposure-dose-response relationships (that is, relative toxicity and no-effects concentrations) of different types of particles by using the same experimental protocol related to a particular health outcome. Finally, to understand the role of PM ultimately and the specific particles' characteristics in the health effects associated statistically with air pollution, it will be necessary to validate hypotheses and exposure-dose-response relationships must be validated in studies that include non-PM pollutants. The increase in toxicity of diesel soot after exposure to O_3 (Madden et al. 2000), for example, suggests the importance of interactions between particles and other pollutants.

The consideration of a multiplicity of characteristics will present a challenge for epidemiological studies. Many of the measures of particle components and characteristics will be highly correlated. In single pollutant models, several of these components might be significantly associated with a health outcome, but it will be difficult to identify those components that might be most highly associated with health outcomes. The ability to discriminate among correlated components will require larger numbers of observations than required to determine significance of components in a single pollutant model. It is unlikely that cross-sectional studies will ever amass sufficient observations to allow one to discriminate among the many characteristics that need to be considered. Time-series studies will require several years of data; alternatively, one could search for study locations where specific pairs of components might be less highly correlated in an effort to determine which component of the pair is most highly associated with the outcome.

An alternative to the consideration of components themselves is the consideration of source categories or source indices. For example, studies have been undertaken in which the health outcomes of individuals living near busy roadways have been compared with the outcomes of those living farther from the roadways. These studies have the ability to indicate the importance of a given source for health outcomes, but they do not allow an understanding of those air pollution components that are most highly associated with an outcome. For example, it would be impossible to learn whether tailpipe emissions of gases or particulates or particulates tied to brake or tire wear would be most highly associated with a health outcome.

Other methods use principal components or factor analysis of the various particulate characteristics in an effort to reduce the number of pollution variables to a set that are not correlated with each other (see topic 10). The difficulties with this approach are that (1) the set of resulting variables might not be easily interpreted, and (2) the set might not be consistent over time and for different locations. The approach also does not identify those specific components that are most highly associated with health outcomes.

RESEARCH TOPIC 6
DOSIMETRY: DEPOSITION AND FATE OF PARTICLES IN THE RESPIRATORY TRACT

What are the deposition patterns and fate of particles in the respiratory tract of individuals belonging to presumed susceptible subpopulations?

Introduction

Dosimetry encompasses several critical links between personal exposures to inhaled PM and the health responses that result from those exposures. Accordingly, an adequate knowledge of dosimetric factors is critical to these aspects:

- A correct interpretation of the exposure-response relationships.
- An understanding of variations in susceptibility to PM effects.
- The ability to develop biomarkers of PM exposure and effects.
- The development of animal models of human responses to PM.
- The ability to extrapolate hazards, exposure-response relationships, and response mechanisms from animals to humans.

- The design and interpretation of experiments using in vitro biological systems.

Among the important dosimetric factors are the portions of inhaled PM that deposit in different regions of the respiratory tract; the influence of both host and PM variables on the amount and site of PM deposition; the effect of PM size, surface, and solubility on cellular doses of causal components; the pathways and rate of clearance of PM from the respiratory tract; the pathways and rates of translocation of PM and PM-derived materials to sites within and outside the respiratory tract; the amounts and sites of retained PM; the tissue and cellular doses and dose rates of PM and PM-derived materials, and the route and rate of excretion of metabolic products of PM.

The relevance of dosimetric issues to an understanding of PM exposure-response relationships for regulatory purposes is readily illustrated by one of the many advances in the understanding of PM dosimetry since development of the 1996 PM criteria document. Epidemiology indicates that individuals having preexisting cardiorespiratory disorders, including chronic obstructive pulmonary disease (COPD), have increased susceptibility to the effects of PM. Kim and Kang (1997) found that the total lung deposition (PM inhaled minus PM exhaled) of 1.0 μm of particles was twice as high in 10 subjects with COPD as in 10 normal subjects exposed under identical conditions. That finding and similar findings with other respiratory disorders strongly suggest that increased dose is one factor that may contribute to increased susceptibility. For example, if two people, one normal and one with COPD, were exposed to environmental PM at the same air concentration, the person with COPD might receive twice the dose as the normal person and thus might suffer twice the effect due to the difference in dose alone and not to differences in response to the PM once deposited. This knowledge of "dose susceptibility," in contrast to the more typical concern for "response susceptibility" (greater response at the same dose), has implications for setting the PM standard, for identifying and protecting susceptible groups, and for developing and validating nonhuman models of human susceptibility.

There have been important advances in knowledge of PM dosimetry since the committee's research recommendations were first published in 1997, but not all issues have been addressed and considerable work remains. This section reviews progress from 1997 to September 2002, based primarily on published literature.

State of Understanding in 1997

The understanding of the fractional total and regional deposition and short- and long-term clearance of PM from the respiratory tracts of normal adult humans and common laboratory animals was well advanced at the time the 1996 PM criteria document was developed. The dosimetry chapter of the criteria document (Chapter 10) included a thorough exposition of the well-understood factors affecting the deposition and clearance of particles ranging from approximately 0.1 to 10 μm in aerodynamic diameter. Organizations such as the National Council on Radiation Protection and Measurements (NRCP) and the International Commission on Radiological Protection, as well as other researchers, had been working for several years to develop mathematical models of PM deposition and clearance, and although several alternative models existed, agreement among them was considerable. Information from physical measurements of lung casts and from experiments with branching tubes had begun to yield refinements of models that incorporated nonuniform airway dimensions and deposition hot spots at airway bifurcations and other perturbations of air flow. Physical measurements of airway casts also yielded data by which differences in PM deposition in adults and children could be inferred. Computational fluid dynamic modeling had begun to yield useful mathematical models of PM flow and deposition in extrathoracic (nose, mouth, oropharynx, and larynx) sites.

By 1997, however, it was obvious that our understanding of PM dosimetry did not adequately encompass the full range of issues that needed to be understood to place the growing evidence for health impacts of environmental PM into context from either the scientific or regulatory points of view. Although personal exposure data were scant, epidemiology was clearly suggesting differences in PM exposure-response relationship effects among subpopulations having different characteristics. Our knowledge of differences in PM deposition, clearance, retention, and translocation among subjects of different ages and genders, and particularly among those having respiratory abnormalities, was poor. It was not clear whether these variables caused differences in dose that exceeded the large normal range of intersubject variability in deposition and clearance.

Although toxicological studies of animals and cells were examined for evidence lending plausibility to the growing and increasingly detailed epidemiological evidence for PM effects, mathematical models for dosimetric extrapolations between humans and laboratory systems were crude and controversial. Emphasis on the development of animal models for

presumed susceptible human subpopulations was burgeoning, but almost no information was available on PM deposition, clearance, dissolution, and translocation in animals modeling human cardiorespiratory disorders. There had been very little study of the contribution of dose variables to the increased responsiveness of susceptible humans or animals. With the growing recognition of the possible importance of the ultrafine fraction of environmental PM (generally considered to be particles of 0.1 μm, or 100 nm, or less in diameter), knowledge of the deposition and fate of ultrafine poorly soluble PM in normal humans and animals was rudimentary and information on the dosimetry of ultrafine PM in abnormal lungs was nonexistent. Moreover, there was virtually no knowledge of the fate of the nonsolid ultrafine condensate "nanoparticles" that were being increasingly recognized in combustion emissions. In the face of emerging evidence for the effects of environmental PM in nonrespiratory sites, and especially in the cardiovascular system, there was poor knowledge of the distribution and translocation rates of ultrafine PM and PM-derived materials to the heart and other organs.

In its first report, the committee noted the importance of dosimetric considerations to the understanding of the relationship between exposures to environmental PM and resulting health effects, and it recommended research on several specific topics to fill information gaps. The committee presumed that ongoing work to refine dosimetric models for normal humans and for extrapolating between animals and humans would continue and thus focused the following recommendations on research issues that it concluded were unlikely to be addressed without directed emphasis:

Deposition

- Determine differences in deposition of PM in the respiratory tract between normal individuals and those having respiratory abnormalities presumed to contribute to susceptibility.
- Obtain quantitative data on lung morphology and respiration of individuals of different ages and genders and having respiratory abnormalities.
- Determine effects on deposition of particle size, hygroscopicity, and respiratory variables in individuals having respiratory abnormalities.
- Develop mathematical models for predicting PM deposition in susceptible individuals, and validate the models by measurements in individuals having those conditions.

- Develop information on interspecies differences and similarities in the deposition of ultrafine PM in abnormal versus normal respiratory tracts.

Clearance and Translocation

- Determine differences in translocation and clearance of PM and bioavailability of PM-borne compounds in the respiratory tract between normal individuals and those having respiratory abnormalities presumed to contribute to susceptibility.
- Determine the fate of deposited ultrafine PM, and determine whether respiratory abnormalities alter the translocation pathways or rates.
- Determine interspecies differences and similarities in the translocation, bioavailability, and clearance of PM in normal versus abnormal respiratory tracts.

What Has Been Learned?

The committee reviewed research progress in comparison to its dosimetry recommendations in its third report (NRC 2001). To a large extent, although more work has been published, the areas of most progress and least progress remain similar at this time. A cohesive dosimetry program as such has not emerged within the PM research agendas of EPA or other research sponsor organizations. Except for emphases on PM dosimetry in humans within the EPA intramural research program and on interspecies extrapolation models at the CIIT Centers for Health Research and its collaborators, most publications have reflected opportunistic dosimetric measurements conducted in association with studies designed to address other primary issues, or they have reflected continuations of model development efforts begun before the committee's recommendations. Although several meaningful advances have been made to correct the lack of attention paid to dosimetry, it will probably require specific attention within funding initiatives to ensure that all the important PM dosimetry knowledge gaps are addressed.

The scope of research within the EPA PM centers program encompasses consideration of dosimetry (Lippmann et al. 2003). Although several abstracts have been presented, the work (as of July 2003) has resulted in few dosimetry publications. Dosimetry of inhaled ultrafine PM

is one of the explicit areas of focus of the University of Rochester Center. That is appropriate because differences in deposition and translocation between ultrafine and larger (fine and coarse) particles are a key issue. The total respiratory tract deposition of different sizes of ultrafine carbon in humans has been studied at rest and during exercise and found to match model predictions (Daigle et al. 2003). Differences were found between the extrapulmonary translocation of ultrafine ^{13}C-labeled carbon and ^{192}iridium particles inhaled by rats. The carbon particles were rapidly translocated to liver and brain (Oberdörster et al. 2002), but few iridium particles were translocated (Kreyling et al. 2002). Research at the New York University Center includes development of techniques for creating airway models and hollow casts by noninvasive X-ray computerized tomography for modeling differences in airway structure and particle dosimetry related to age, gender, and airway abnormalities, but the work is still under developmental at this time. Total deposition of concentrated ambient particles (CAPs) inhaled by dogs has been measured at the Harvard University Center in conjunction with studies of cardiac effects. Investigators at the Southern California Center have worked to improve estimates of local tissue doses at deposition hot spots to place doses used in in vitro studies in better context. The above research approaches are appropriate considerations for applying known dosimetric techniques in health studies of PM and advancing knowledge of PM dosimetry in humans and animals. More publications can be anticipated in the future.

Progress in addressing the committee's recommendations can be measured in part by the number of dosimetry-related publications since development of the 1996 criteria document. An October 2002 literature search produced a total of 160 journal articles that were related wholly or in significant part to PM dosimetry and that were published during 1997 and up to September 2002. Although a few of the articles were reviews, most reported original results. Of course, there have been a few dosimetry-related publications since that literature survey. The total number of papers is a substantial total research output, and one commensurate with the overall level of effort envisioned by the committee's recommendations. However, because only a minority of the papers dealt with issues falling within the committee's specific recommendations, the literature reflects an insufficient effort to encompass the scope of knowledge gaps identified by the committee.

Several of the 160 papers dealt with more than one issue; thus, the following categories and percentages include overlapping citations. Approximately 50% of the papers dealt with deposition measurements and

refining predictive deposition models for normal humans, the primary emphasis being on the effect of breathing pattern and PM size and somewhat less on the effects of gender and age. Of those, approximately one-half dealt solely with models, and few of those included validation of the models against actual measurements. Nearly all deposition measurements included only total respiratory tract deposition; other than refinement of models, there was little emphasis on deposition in different regions of the respiratory tract. Eight papers examined the effect of PM variables, including size, hygroscopicity, cloud effects, and gravity, on deposition in normal subjects. Four papers dealt with total or airway deposition of ultrafine PM in normal humans and the effects of breathing pattern, gender, and exercise but no actual measurements in subjects with respiratory abnormalities.

Fewer than 10% of the papers dealt with deposition measurements and models for subjects with respiratory structural or functional abnormalities. The conditions examined included COPD, cystic fibrosis, asthma, and induced airway constriction. Some, but few, of the mathematical modeling efforts attempted to incorporate abnormalities, and none included validation against actual measurements. No work on models for interspecies extrapolation of deposition in abnormal lungs was evident.

Approximately 40% of the papers addressed PM clearance, translocation, and retention. Measurements were about equally divided among normal animals and humans, individuals having respiratory abnormalities, and mathematical models. Although these reports encompassed a diverse range of issues, methods, and particle types, they represent at least incremental advances in the understanding of the fate of deposited particles. The majority of reports resulted from animal studies; however, only two dealt with interspecies extrapolation of PM clearance, and none dealt with interspecies extrapolation of translocation. Among the papers reporting results from humans, five reported the amount, location, and nature of PM retained in lungs at autopsy. Only a few dealt with translocation of PM, PM-derived materials, or biological reaction products outside the lung.

Key Advances in Understanding PM Dosimetry

Arguably, the greatest policy-relevant advance in understanding PM dosimetry since the last PM criteria document (EPA 1996) has been the demonstration that respiratory abnormalities tend to increase the deposition of inhaled $PM_{2.5}$. The increase in deposition can be substantial; for example, twofold increases in total deposition have been measured in people with

COPD (Bennett et al. 1997; Kim and Kang 1997). It appears that most, if not all, airway abnormalities act to increase deposition (Kohlhäufl et al. 1999). In addition, increasingly sophisticated deposition models indicate that abnormalities of respiratory structure and airway function also tend to decrease the homogeneity of PM deposition and increase deposition at localized hot spots. Such deposition might even further increase doses in localized areas (for example, see Martonen et al. 2001). It is conceivable that the increased susceptibility of some people with respiratory abnormalities is due to differences in exposure-dose relationships rather than to abnormalities of dose-response relationships. This knowledge raises the concept of "dose susceptibility" in contrast to "response susceptibility" and bolsters the importance of dosimetry in resolving PM health risks.

Another advance is further demonstration that children may receive a higher dose per unit of respiratory surface than adults (Musante and Martonen 2000). Another is the better definition of deposition differences between women and men, and the effects of exercise and different breathing patterns (Jaques and Kim 2000). Together, these advances provide a substantially improved understanding of PM exposure-dose relationships and the range of variability in deposited dose among the population.

There has been a substantial refinement of mathematical models for estimating PM deposition, taking into account an expanded range of variables having to do with age, gender, physical structure of the airways, airway abnormalities, ventilation rate, respiratory pattern, and PM characteristics (Musante and Martonen 2000; Segal et al. 2000, 2002; Broday and Georgopoulis 2001; Lazaridis et al. 2001). These refinements purport to allow estimates of total and regional dose in different subpopulations to be made with improved accuracy, although it remains unclear whether the magnitude of the refinements are significant compared with the magnitude of interindividual variability. There have been particularly noteworthy advances in models for extrapolating deposition and retention from rodents to humans, improving on previous approaches by taking into account species-specific inhalability, airspace dimensions, variations in path length, surface area, and macrophage numbers (Hofmann et al. 1999; Miller 2000; Winter-Sorkina and Cassee 2002). This work has resulted in readily available, user-friendly software for estimating dose metrics and extrapolating doses and "equivalent exposures" between humans and rats (Price et al. 2002).

The understanding of PM deposition in extrathoracic (upper airway) portions of the respiratory tract has improved, thus refining understanding

of the importance of extrathoracic deposition to the limitation of dose received by the lung.

There are now more data on the deposition of ultrafine PM; however, there have been only a few studies and understanding remains inadequate. The recognition of the predisposition for ultrafine PM deposition in the nose and large airways has helped place the dose received in alveolar regions in a clearer context. Although ultrafine PM can certainly reach the alveolae deep lung, it is now better appreciated that alveolar deposition does not necessarily predominate the dose of ultrafine PM more than the dose of fine PM. Even within the ultrafine size range, there are size-related variations in alveolar deposition. Total deposition of inhaled ultrafine carbon, for example, was found to vary with particle size, in agreement with predictive models (Daigle et al. 2003).

The understanding of the behavior of ultrafine PM after deposition, especially its transport to blood and other organs, has been enhanced somewhat but remains sketchy. Ultrafine particles are difficult to track, and progress has largely been limited by the rate of development of tracer particles that are sufficiently insoluble that detection of the label can confidently be considered detection of particles. For example, Nemmar et al. (2002) used ^{99m}Tc-labeled ultrafine carbon particles and demonstrated passage of the radiolabel to blood and liver, but the extent to which the label was associated with PM remained in question. Some labels can be more confidently assumed to remain with the particle. Using ^{13}C-labeled carbon particles, Oberdörster et al. (2002) found particles to translocate rapidly to liver and brain after inhalation by rats. On the other hand, Kreyling et al. (2002) found little translocation of ^{192}Iridium particles after inhalation by rats. Continued studies of reasons for the differences among these observations and the quantitative kinetics of the translocation of ultrafine particles are likely to advance knowledge.

There has been little progress in understanding the translocation of other particles or particle-borne compounds outside the lung. Urinary excretion of PM-derived compounds was reflected by the finding of increased urinary hydroxypyrene in carbon-black workers (Tsai et al. 2002) and increased urinary nickel excretion in workers exposed to nickel-containing PM (Werner et al. 1999). A biological impact of PM-derived agents in nonrespiratory sites was demonstrated by increased DNA adducts in circulating white blood cells of workers exposed to combustion emissions (Lewtas et al. 1997).

The advances summarized above are largely reflected in the dosimetry

chapter (Chapter 6) of the June 2003 external review draft of the PM criteria document (EPA 2003a). With the exception of the lack of mention of extrapulmonary translocation of ultrafine particles, these issues were also appropriately brought forward in the synthesis chapter (Chapter 9) of the criteria document.

Synthesis

The increase in funding for PM research recommended by the committee has bolstered PM dosimetry research and resulted in greater advances than would likely have occurred otherwise. However, there is little evidence that a cohesive EPA PM dosimetry program aimed specifically at addressing the committee's recommendations has been implemented or that funding has been directed specifically toward dosimetry. There has been investment within the agency's intramural program in assessing PM deposition in certain presumed susceptible groups and improving PM deposition models, but it is not clear that the intramural program has been directed to address other issues that have lacked attention.

There has been modest integration of dosimetric considerations or dosimetry research into the design and interpretation of extramural research funded by EPA through both the PM centers and STAR programs. It is not evident that other sponsors supported particle dosimetry as a focus of research, other than research in support of inhaled pharmaceuticals. Research sponsors could have, but have generally not, ensured that toxicological research be conducted within realistic dose ranges and that the dose, as well as the response, be characterized in studies using animal models of susceptible humans.

Decisionmaking Value

The information gaps addressed by the committee's research recommendations were selected from among the much wider range of dosimetric uncertainties on the basis of their relevance to PM management policy decisions. The issues remain policy relevant at this time. Understanding the relationship between PM exposure and dose and between PM dose and effect is important both for selecting the indicator for the standard (for example, the most relevant PM size ranges) and for setting the level of the standard (for example, considering differences in exposure-dose relationships among subpopulations having different susceptibilities). Understand-

ing the contributions of dose to the increased susceptibility of animal models of susceptible human subpopulations is important for placing evidence for plausibility of causation into context. Confidence in extrapolating PM dose-response relationships from animals to humans is integral to the confidence with which human health hazards and exposure-dose-response relationships can be inferred from data from animals. Such extrapolations have an impact on identifying the most important PM characteristics and on setting the level of the standard.

Information Expected in the Near Future

On the basis of ongoing research, additional information on the kinetics of translocation of deposited ultrafine particles outside the lung is assumed to be forthcoming over the next 2-5 years. Although some attention is now being directed toward the importance of nonsolid, combustion-origin ultrafine particles, it is not evident that this work will include determining the fate of such material after deposition. There are ongoing efforts to improve mathematical and physical models of the respiratory tract, and some improvement of dosimetric models are anticipated. Although gaps will remain, the ability to estimate differences in dose related to age, gender, activity, and respiratory tract abnormalities should largely be adequate for regulatory risk assessment over the next few years. Without specific emphasis from EPA and other research sponsors, one cannot predict that there will soon be substantial improvement in the understanding of particle dosimetry in animal models of susceptibility or in the understanding of the translocation of materials dissociated from deposited particles.

It is not clear what new dosimetric issues may emerge over the next few years, but issues regarding specific PM types, components, and mechanisms are likely to be raised as new findings emerge. Examples can be drawn from the issues that have already emerged but are not yet adequately addressed. During the past several years, the finding that cardiovascular effects might constitute a greater health burden than respiratory effects has raised questions about the translocation of PM and PM-derived material outside the lung via the vasculature and along neural pathways. The broadening recognition during recent years that nonsolid, organic-based ultrafine PM constitutes a substantial portion of ultrafine combustion emissions has raised questions about the fate of that material once deposited; for example, the relationship between the lipid solubility of the material and its persistence in particulate form needs to be examined. The finding that PM deposition is increased in abnormal lungs has emphasized the need to

determine deposition and clearance in animal models of susceptibility. None of these is a strictly new issue, but based on work under way and the issues being identified, it can be expected that the next few years will see advances in these areas.

It can be hoped that to an increasing extent, dosimetry will be viewed as a unifying factor facilitating conceptual and experimental linkages among researchers dealing with PM exposure, effects, and predictive models. Dosimetry offers a weak goal as an end to itself but comprises a powerful "common currency" in linking research issues and approaches. Dosimetric variables should be an integral part of increasingly sophisticated models for predicting relationships between environmental concentrations and public health burdens among specific subpopulations.

Major Remaining Uncertainties

The issues identified as inadequately addressed in the committee's last report (NRC 2001) generally remain the key areas of need at this time. The committee's recommendations focused largely on dosimetry in abnormal respiratory tracts, and although advances in this area are considerable, the majority of dosimetric research has continued to address dosimetry in normal subjects.

Despite the important findings regarding total PM deposition in subjects with respiratory abnormalities, a sufficiently broad range of issues has not been addressed. There is virtually no information on deposition in lungs of older normal subjects. There is little information on regional and local deposition, including deposition hot spots, in lungs of susceptible humans and little evidence that this information is being developed. There has been almost no work on PM deposition, clearance, and translocation in animals having natural or induced conditions modeling susceptible humans. As a result, the contribution of dosimetric differences to the observed differences in response, which by default are attributed to differences in response mechanisms, is unknown. There has been little effort to validate the increasingly sophisticated deposition, clearance, and translocation models and interspecies extrapolation models against actual measurements. Although considerable advancement has been made in the extrapolation of dosimetry from rats to humans, the ability to make interspecies comparisons of PM dosimetry across other species, especially ultrafine PM, is still not adequate. Although the growing information base points toward its potential importance, an adequate understanding of the translocation of ultrafine PM either within or outside the respiratory tract has not been developed.

There is also no understanding of the fate of deposited nonsolid ultrafine condensate "nanoparticles," despite the fact that this material is a ubiquitous component of the vehicle emissions that continue to be a source of regulatory concern.

What Remains To Be Done?

Although emphasis and expenditures related to dosimetry have been limited, progress has been made in the understanding of particle dosimetry. The developing understanding of dosimetric differences among individuals and locations within the respiratory tract need to be linked to health outcomes and mechanisms. Potential differences in fractional and regional deposition between older subjects and young adults remain uncertain. Considerable uncertainties remain regarding the rates of translocation of PM and PM-borne compounds to nonrespiratory organs. Clearance has been less well studied than deposition, and the effects of gender, age, and respiratory abnormalities on clearance remain largely unstudied. As stated in its previous reports, the committee still identifies dosimetry in animal models of susceptibility as important to interpreting laboratory results and extrapolating them to humans.

RESEARCH TOPIC 7
COMBINED EFFECTS OF PARTICULATE MATTER AND GASEOUS COPOLLUTANTS

How can the effects of particulate matter be disentangled from the effects of other pollutants? How can the effects of long-term exposure to particulate matter and other pollutants be better understood?

Introduction

From the earliest days of concern for air pollution, ambient pollution has been recognized as a complex mixture of PM and gases that come from primary combustion and the physical and chemical transformations undergone by these emissions. The earliest studies focused on testing whether adverse health effects could be associated with measurements of single indicators of pollution considered as representing known sources. For example, the combustion of fossil fuels was recognized as producing smoke

and SO_2. Similarly, mobile-traffic sources are known to produce carbon monoxide (CO), particles, and other gases that react photochemically with sunlight to produce oxidant pollution. The associated effects were generally recognized as not being due to the single indicator measured but rather that the indicator might be serving as a surrogate for the total complex mixture of pollutants. The passage of government statutes to control air pollution by setting limits on specific components shifted scientific attention to the risks of several major indicator pollutants and the potential for interactions among the pollutants to reduce synergistic actions. Early ordinances in the United Kingdom focused on smoke and SO_2. The Clean Air Act Amendments of 1970 (P.L. 91-604) identified individual pollutants as being of concern both in sections of the act dealing with criteria pollutants and in sections concerned with hazard air pollutants. In addition, the act recognized that complex mixtures would be of concern (Clean Air Act, Section 103 [1970]) with regard to control measures. That recognition was an important caveat, because it raised a series of questions about regulators' consideration of strategies for implementing control measures most efficiently. The toxicity of a mixture might depend on interaction among its components, and the degree of interaction might vary with the mixture's makeup. Progress, however, in understanding combined or multiple pollutant effects has been made slowly, as the methodological difficulties in studying combined pollutants have been substantial (Samet et al. 2000a)

Research has been carried out to address the combined effects of pollutants. Early toxicological studies in the 1950s and 1960s in an infectivity model in rabbits suggested that the combination of inert particles and NO_2 led to rapid and excess mortality when these agents were given in combination rather than separately (Boren 1964). One of the earliest controlled toxicological exposure studies of exposure to multiple pollutants was initiated by the National Air Pollution Control Administration, which became a part of EPA. The study, carried out in Cincinnati, involved long-term exposure of beagle dogs to a complex mixture of air pollutants designed to simulate urban air pollution, including the use of vehicle exhaust and ultraviolet radiation to simulate the effects of sunlight. After exposure was terminated, the dogs were moved to the University of California at Davis for detailed physiological and pathological evaluations. The levels of effects detected were modest, despite exposures to high concentrations of pollutants. These findings emphasized the challenge faced by experimentalists in first characterizing an appropriate model of effect, whether dealing with laboratory models or human subjects, for health outcomes that are more likely to be prominent in susceptible individuals and that even then have a low incidence.

With regard to epidemiological approaches, possible independent effects of particles and gases have generally been addressed by selecting study sites where the air pollution mixtures have sources for which exposures to gases and particles are not correlated. Alternatively, multivariate analyses taking account of multiple pollutants have been used to trying to partition the effect from a specific class of pollutant from the effects of other pollutants measured simultaneously in that particular region.
Any gain from combining results from numerous studies is limited by the difficulties in defining either exposure or outcome. One of the difficulties related to the lack of uniformity of quality control results from the involvement of a multitude of groups with varied levels of experience in the collection of the data. Another problem is the practical difficulty of measuring exposure adequately. Often only the major components of exposure are measured, and even in those cases, not all pollutants are assessed in the same time scale. Because of the difficulty of controlling combined exposures, few data have been accumulated to document the effect of these combined exposures.

One of the earliest successful efforts to utilize cities with different air pollution profiles in a large-scale epidemiological study was the Harvard Six Cities Study (Ware et al. 1986). This study followed the respiratory symptoms and pulmonary function of children and adults in six communities over a period of 12-18 years. Mortality in adults was related to annual averages of ambient pollutant measures. The results from that study, especially with regard to health effects of PM, are now well known (Dockery et al. 1993). A key contributor to the success of the study was the decision made at the outset to monitor multiple pollutants, including different size fractions of PM.

Another example is the twelve communities study in Southern California (Peters et al. 1999a,b). Again, the incorporation of monitoring multiple pollutants in the communities selected to provide a gradient of individual pollutants for children who were followed repeatedly with respiratory health questionnaires and pulmonary function measures has proved key to interpreting the health effects findings

Toxicological studies to explore mixtures have used three distinct approaches: (1) factorial design studies that have used different pollutants sequentially or in combination; (2) exposures to complex mixtures modified by the removal of one or more pollutants at a time; and (3) a matrix approach in which multiple pollutants are evaluated for total effect. Because of the small number of animals studied, the exposures have been for the most part carried out at extremely high concentrations, and the relevance of the findings to human exposures has been questioned. Similarly, human

clinical exposure studies to combined exposures have also been small.

In summary, until 1997, few toxicological or human clinical exposure studies were designed to assess the combined effect of two or more pollutants. Although the short-term time-series studies used different locations where pollutant mixtures were hypothesized to be different because of different sources, specific measures of the regional mixtures were often not made. Thus, the committee made a major recommendation that more work on specific measured mixtures and better regional monitoring be conducted.

State of Understanding in 1997

To understand the impact of combined exposures requires separating the components of exposure as well as considering the potential of different mixtures having different effects in different at-risk groups. The committee divided the topic into two broad approaches: (1) determining how effects of PM could be disentangled from the effects of other pollutants in relatively short-term exposures; and (2) determining how the effects of long-term exposure to PM and other pollutants could be better understood in relationship to particular disease outcomes.

Some of the work necessary to answer these issues was already under way in 1997. Major sources of particle pollution mixtures have singular signatures. However, the simple characterization of sources does not provide sufficient information to determine the chemical characteristics of the pollutant mixtures nor does it allow for identifying the putative agents in the mixtures. The identification of the pollutant simply as coming from mobile traffic sources or stationary power plants, although perhaps useful from a regulatory prospective, does not allow the investigators to identify putative components and says very little about the gaseous pollutants that might accompany any given source of particles. The committee believed that new data would need to be generated to better characterize sources and the mixtures contained in these sources. For that reason, the committee made a sustained effort to keep informed about the EPA program committed to setting up "supersites," or "speciation sites," and to link these sites where possible to ongoing or newly developed epidemiological studies (see topics 3 and 4).

There are "natural experiments" where changing patterns of sources of pollution mixtures are brought about by changing political or economic conditions that present opportunities for understanding changing mixtures. The classic examples of modern studies of this kind are the studies of Pope in the Utah valley where a steel mill suspended operation, and Pope was

able to measure children's respiratory experience before, during, and after the shutdown (Pope 1989, 1991). These are experiments of unusual opportunity and are difficult to plan; however, such data provide stronger evidence for causality. The committee's recommendation was to be prepared to explore these opportunities should they occur. In such settings, measurements of more than PM would be important to assess the combined effects of mixtures. The only way to characterize the mixed effects would be to have sufficiently accurate measures of the components of the mixtures and to synthesize those mixtures for toxicological studies in appropriate animal models and for clinical studies in potentially susceptible subjects.

Parallel investigations of multiple cities or locations with different pollution characteristics provide an opportunity to explore particulate effects in association with different concentrations of other pollutants. Several studies had used this technique, and despite different sources, similar findings generally were found where PM by weight was used (Schwartz and Zanobetti 2000). However, the more measures used to assess the pollution mixture, the greater the attenuation of the PM effect; on some occasions, the effect could be attributed to the gaseous component as readily as to the PM (Mar et al. 2000; Moolgavkar 2000; Sarnat et al. 2001). That result suggested that studies of that kind needed to be repeated with more uniform measures of the mixtures, again pointing to the importance of using super-sites and speciation sites along with populations at risk to answer these questions.

With regard to long-term studies the only studies available in 1997 were the Harvard six city study and the American Cancer Society' Cancer Prevention Study 2 (Pope et al. 1995). However, even these studies were not able to apportion risk to pollutants other than PM. The reanalysis that was undertaken to first validate the findings of these two studies and the subsequent additional analyses carried out independently and by the original investigators essentially confirmed the original findings. The committee estimated that it would be much longer than 5 years before additional prospective cohorts would be assessed for mortality; however, the committee was aware that several additional cohorts were under observation (see below).

Few controlled exposure studies of realistic ambient concentratioins of mixtures of pollutants had been carried out before 1997. Findings of one study suggested that the particulate effect was enhanced after O_3 exposure (Frampton et al. 1995); however, these exposures were carried out in sequence rather than simultaneously. Animal studies involving doses considerably higher than ambient concentrations suggested additive effects (Kimmel et al. 1997; Jakab et al. 1996). It is important that most of the

earlier controlled studies had used simple combinations of two pollutants rather than true ambient mixtures.

What Has Been Learned?

Existing databases on the subject of understanding the impact of mixtures on health were assessed by evaluating the HEI database (HEI 2002a). Several studies have been started and completed since 1997. However, most of the investigations begun after the committee's initial set of recommendations are still under way and to date have produced only minimal results as indicated below.

The portfolios of each of the recently funded EPA PM centers direct part of their research activities toward understanding the impact of mixtures. In addition, both epidemiological and toxicological projects funded by the California Air Resources Board are attempting to identify the impacts of mixtures on morbidity and mortality, the natural history of asthma, and the histopathological changes in the airways of rats. Additional studies of short-term effects are being carried out in time-series studies funded by government agencies in the United Kingdom and Canada and by the European Commission. Other studies not included in the HEI database are supported by components of National Institutes of Health.

The topic of mixtures was assessed by key words in a database created by this committee by abstracting all the references used in the April 2002 criteria document and classifying them by the 10 priorities identified in our first report. Abstracts and, where appropriate, the original articles that appeared to have been started and completed since 1997 were reviewed by the committee, and it made a judgment on whether the new data were applicable to the posed questions. Several hundred papers were identified in the EPA criteria document, and the exercise was further reduced to identifying articles that were used in the summary chapter of the criteria document (Chapter 9). Over 100 studies were cited as using toxicological or epidemiological methods. Among those, about 25% were toxicological, and of the total that were toxicological or epidemiological, about 20% dealt with mixtures.

Several new studies that have dealt with estimates of sources have been published (Laden et al. 2000; Ramadan et al. 2000; Monn 2001). Those that have assessed long-term effects have suggested that both particles and gases appear to be related to both excess morbidity and mortality, but none of these studies has actually assessed the combined effects of mixtures. In the more recent analyses of acute morbidity and mortality, the

observations have been mixed, with different pollutants producing different effects. European studies have suggested that the effects of mobile-source pollutants are dominant over those of stationary-source pollutants; however, the pollutant measures (CO and NO_2) have been interpreted as potential surrogates for motor vehicle exhaust, and potentially diesel exhaust (Roorda-Knape et al. 1998; Touloumi et al 1997; Burnett et al 2000). In other studies in areas where diesel exhaust is not dominant (for example, Los Angeles), traffic pollution has been associated with symptoms and respiratory effects in children (Peters et al. 1999a; 1999b). In all of the cases, the findings cannot be interpreted as the effect of mixtures, as the mixtures have not been well characterized.

Only one study (Herbarth et al. 2001) was identified in which changing concentrations of TSP and SO_2 since 1989 in East Germany were correlated with evidence of changing rates of bronchitis in children. In this study, the concentration of SO_2 dominated, and the effect of TSP was less important unless SO_2 was increased. Other studies of this region are ongoing or have recently been completed, and results using more up-to-date measures of exposure can be anticipated in the next year.

Several studies from NMAPPS (Samet et al. 2000b,c) reported on multiple locations with PM_{10}, O_3, CO, SO_2, and NO_2 measured similarly in up to 90 cities. After controlling for the various pollutants, they reported that total mortality and cardiovascular and respiratory disease mortality and morbidity remained significantly high for PM_{10}. Recent reports have modified these original results to take into account the difficulties found in the execution of computer programs used in analyzing these data. For the most part, the directions of the estimate of the impact remains about the same, but the magnitude of the effects has been reduced (Ramsey et al. 2003a,b).

A few studies were identified that assess long-term effects of particulate pollutants. These varied between cross-sectional assessments (Braun-Fahrländer et al. 1997; Zemp et al. 1999) of symptoms and pulmonary function attributed to lifetime exposures measured over varying periods of time and assumed to be applicable to lifetime exposure, actual measures of change in pulmonary function over relative short term (3 years) (Frischer et al. 1999) of monitored exposure, and detailed repeated evaluations for up to 20 years (Abbey et al. 1999; Beeson et al. 1998). Although some of these studies attempted to separate the particulate from the gaseous pollutants, the results were no different for the most part from those of previous studies, except, as indicated above, the finding in the European studies of the dominance of the mobile sources over stationary sources on the health effects observed.

Much of the work on toxicological exposures continues to be with two-pollutant models. Three studies reported effects of combined O_3 with particles. For older animals, consistent changes were noted when O_3 was combined with PM_{10} (Bolarin et al. 1997). Similar results were seen in two other studies in rats. A comparison of dogs living in polluted and less-polluted areas in Mexico, noted a variety of pathological changes consistent with lung injury among the group with greater pollutant exposure (Calderón-Garcidueñas et al. 2001a,b). Unfortunately, the details of the exposure are not well characterized. Newer studies have assessed cardiovascular outcomes in rodents, dogs, and several small studies of humans exposed to two-pollutant models. In rodents, depending on the route of administration of the pollutants, the results have not been consistent, in that the added effect of O_3 and PM has an impact on different levels of airways. In humans exposed to concentrated ambient particles (CAPs) plus O_3, high-resolution vascular ultrasonography showed increased brachial artery vasoconstriction compared with that from filtered air (Brook et al. 2002).

Most of the new knowledge since 1997 has been directed at exposure and on the effects of particles on health, as assessed through toxicological and epidemiological research. Short-term health effects measured in time-series studies have provided a boundary of the level of effects that might be seen in high-risk groups. Longer-term studies have demonstrated through reanalysis that the findings were robust and not likely to vary much with manipulation of the data. Several panel studies in potentially high-risk groups of subjects have been followed in real-world settings and monitored for cardiovascular abnormalities that have included changes in heart-rate variability, blood pressure, and heart rate. These investigations have consistently shown changes in cardiac responsiveness associated with exposures. Responses have been noted not only with time-series studies of cardiovascular mortality and morbidity but also with what are believed to be autonomic cardiac responses manifest by increases in pulse rate and decreased heart-rate variability. In addition, changes have been noted in cardiac rhythm, increased risk of myocardial infarction, and changes in serum markers of inflammation that are correlated with increased risk of heart attacks. Similar effects, except perhaps more dramatic because of higher levels of exposure, have been seen in animals. However, the impact of mixtures has not been significantly advanced in the analyses done in these studies. Few of the studies have specifically made sufficient measures of the mixtures to which subjects, patients, or animals have been exposed. Thus, whether pollutants act synergistically or additively has not been studied sufficiently. What can be said, however, is that after taking account of other pollutants in many analyses, the effects of PM, generally measured

as $PM_{2.5}$, remain positive and significant. As indicated above, few of the studies in free-living environmental settings have sufficiently partitioned the effects noted into specific particle species and the gases that are also present. Similarly, the toxicological studies that have used mixtures and have been able to quantitate changes in response by the nature of the mixture have generally involved only two putative substances. Additional studies are under way to explore in a matrix setting the impact of more realistic mixtures of ambient pollutants.

To better understand the effects of PM and other pollutants acting together in mixtures, both toxicological and epidemiological studies are needed. In both human and animal studies, health effects have been confirmed for PM after adjusting for other measured pollutants. The consistency of findings and the concordance of the evidence suggest that there is an effect of PM by itself and that further research should address how that effect is modified by other pollutants. An important recognition has been that research into understanding the health impacts of mixtures will require increased collaboration between investigators trained in a variety of disciplines. What will be required is more organized multidisciplinary approaches so that the data needed will be collected in the most efficient manner.

Scientific Value

Although the advances over the past 6 years on the potential impact of ambient air pollution have broadened understanding and confirmed and suggested a causal role for PM on both the respiratory and cardiac systems and on the possible role of particulate pollutants on inflammation, few advances have been made in understanding which specific additional pollutants in association with the PM mixture are additional putative agents. The studies have convinced investigators that PM is associated with adverse health effects. Significant additional research has been stimulated by these results. The results also have stimulated research that attempts both to understand the components of the air that might be the putative agents and to investigate the potential mechanisms of response (see research topic 9).

Decisionmaking Value

The data published to date on the combined effects of pollutants or the comparative potency of mixtures that simulate ambient atmospheric pollu-

tion are not yet sufficient to prompt a change in decisionmaking, in comparison with the state of the evidence in 1997. Clearly, additional data collection remains an important objective because strategies used to ameliorate pollutants might depend on identification of the specific agents that have health effects. However, because of the difficulties in designing studies that can actually separate the effects of several putative agents in the air pollution mixture, this goal may not be achievable until rapid, inexpensive technology for monitoring exposure both over the short periods of experimental observation and during long-term follow-up of potentially at-risk subjects is available and used.

Information Expected in the Near Future

To assess this question, the committee used, in part, the inventory created by HEI, which started gathering from investigators, project offices, and agencies listings of funded research undertaken and classified by the one or more of the original 10 research topics outlined in our first report. Using the available search tools on the HEI database and judgments obtained by reviewing the abstracts, the committee constructed summaries of activities related to the combined effects of pollutants. Summarizing the data through September 2002, they identified 18 epidemiological studies, 14 toxicological studies, and 2 clinical studies as attempting to assess combined exposures of particles and gases. For the most part, those studies are, at best, two-pollutant models that are being done experimentally with either toxicological studies or studies of controlled exposures. Studies with CAPs are being used to represent a form of mixture that is dependent on local sources. In those studies, the local gases may or may not be filtered out; however, little has been done to date in these studies to characterize the content of the mixtures. More promising are studies being done at designated supersites, or speciation sites, where detailed monitoring and characterization of exposure are possible. Unfortunately, most of those studies are still in their infancy, and it will be another 2 or 3 years before many of the results are available. In addition, because of the varied and complex nature of data being collected at the supersites and the relative lack of communication between the monitoring community and potential health effects investigators, to date these resources have not been exploited to their full potential. Furthermore, the speciation sites are scheduled to close down over the next year, and unless local support is found to maintain at least a core of mea-

surements, they will not be as useful as they might have been for health-related work.

Major Remaining Uncertainties

Over the past 6 years that level of uncertainty has been reduced, but only slightly. What is clear from the various reviews of the literature, symposia, and reports at recent meetings is that once beyond a two-pollutant model, separating out effects of components of mixtures of pollutants will be extremely difficult. Significant developmental work remains to be done to permit the creation of realistic mixtures of pollutants that represent more than the combination of a single particle and a single gas and to know with certainty how any particular artificial mixture relates to levels of pollution in the real world. The best opportunity for overcoming this uncertainty will come from better monitoring of specific exposures and better utilization of differences between environments where these measures have or can be made. CAP studies of real-world ambient pollutants, in which both gases and particles can be characterized and used in toxicological and clinical studies, may be helpful. For the most part, these studies have yet to have been performed in adequate numbers of animals or humans and in enough different regions of the country to have any sense of variability and diversity of response.

What Remains To Be Done?

The committee's review found some new direct evidence related to topic 7, although the newer observational studies have continued to demonstrate an independent effect of particles that is robust to statistical adjustment for other pollutants. In its general review, the committee noted that assessments of effect modification in the epidemiological studies have provided little evidence that the effect of PM varies with other major pollutants in ambient air. Toxicological research, although limited, provides generally consistent findings. The committee concludes that further research is needed to address research topic 7, but acknowledges the challenges in carrying out such studies whether based in observation or experiment. Modification of the effect of PM by other pollutants, particularly O_3, can be more powerfully explored in planned larger studies, such as exten-

sions of the NMMAPS approach. Better characterization of the mixtures contained in source-oriented exposure studies would make such studies more valuable. Understanding better why some mixtures from different sources have particular effects in different diseases would aid the mechanistic explorations of the basis for effect modification.

RESEARCH TOPIC 8
SUSCEPTIBLE SUBPOPULATIONS

What subpopulations are at increased risk of adverse health outcomes from particulate matter?

Introduction

A number of subpopulations have been identified from earlier studies as particularly susceptible to the health effects of specific air pollutants and air pollution in general. These groups include people with asthma, COPD (for example, chronic bronchitis and emphysema), or coronary heart disease; older people; young children; and possibly fetuses. They are presumed to be at increased risk from PM air pollution as well. Air quality standards are intended to protect the health of the most vulnerable members of society as well as the general population, so it is imperative that subpopulations at increased risk from PM pollution be identified and the nature and magnitude of their risk understood.

People with preexisting disease conditions of different organ systems are most likely to be adversely affected by particulate air pollutants. Genetic disposition for susceptibility seems to play a role, as shown for active and passive smokers (Oryszczyn et al. 2000). Interindividual responses to inhaled air contaminants can vary significantly even in healthy people. Associations between very small incremental increases of PM and significant adverse health effects, however, may occur only in some portion of a susceptible population. Variations in PM exposure, PM dose, and host-related factors can cause exposed people to be more susceptible (see Figure C-1).

Susceptible populations can be defined as subpopulations who are particularly susceptible to the effects of air pollution based on one or more of the following factors: (1) increased exposure due to longer-duration

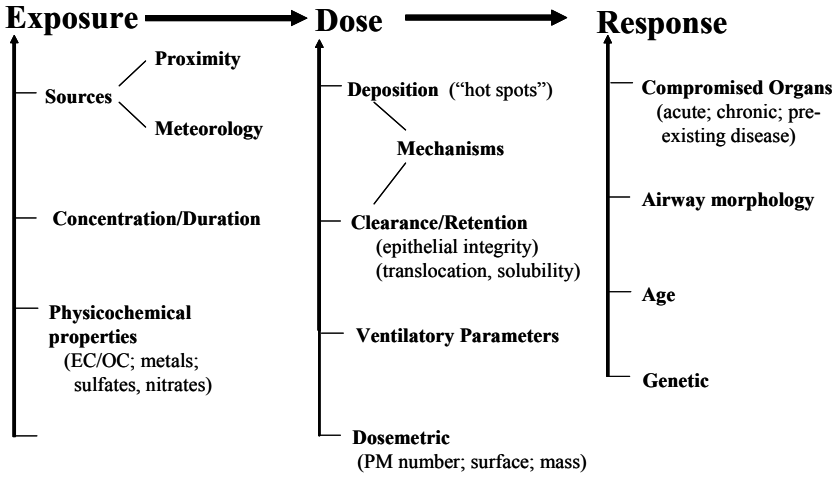

FIGURE C-1 Factors within the exposure-dose response paradigm that influence susceptibility. Abbreviation: EC/OC, elemental carbon/organic carbon.

and/or higher-than-normal pollution concenctrations; (2) higher delivered dose due to physiological factors; and (3) a greater health response than the general population to a given dose of air pollution.

People can be at increased risk from increased exposure to air pollution due to the amount of time they spend outdoors or their proximity to pollution sources. Examples of subpopulations with increased exposure to air pollution include outdoor workers, children playing outdoors, tollbooth and traffic workers, and people living near bus depots.

Certain subpopulations are at increased risk from air pollution due to factors that result in a higher than average dose of pollution delivered to affected parts of the body for an equivalent amount of exposure. Examples of subpopulations that are at risk from higher pollution doses are children, athletes, other exercising adults and children, persons working outdoors, and people with chronic obstructive lung disease.

Finally, certain subpopulations respond with greater than normal intensity to a given dose of air pollution because of genetic makeup or preexisting disease (Oryszczyn et al. 2000). Examples of subpopulations with a greater than normal response to air pollution include people with asthma or chronic lung disease, people with cardiovascular disease, and people who are allergic or atopic.

In its first report, the committee emphasized that the limited knowl-

edge about risk factors in susceptible subpopulations prevented the development and validation of effective models for exposure assessment to provide the basis for prediction of actual doses. A need was pointed out for controlled human exposure studies and the development of appropriate animal models (that mimic human respiratory and cardiac diseases) to obtain the essential data for exposure and dose modeling in the susceptible subpopulations.

State of Understanding in 1997

By 1997, numerous publications already had reported significant associations between PM_{10} and $PM_{2.5}$ and morbidity and mortality in susceptible subpopulations. Elderly people and persons with preexisting respiratory and cardiovascular conditions had been studied more than other groups. However, most researchers did not pursue these results until new cardiovascular effects were observed in several recent studies. High pollution episodes were especially well known to cause high mortality and morbidity, and occupational exposures to relatively high concentrations of soluble PM components were known to cause acute and chronic noncancer effects and respiratory and extrapulmonary cancers. What was not known was whether low concentrations of ambient PM cause observed morbidity and mortality. Small, incremental increases in exposure concentrations of ambient PM_{10} and especially $PM_{2.5}$ were observed to cause acute morbidity and mortality in susceptible subpopulations.

Epidemiological studies before 1997 had been conducted on infants; children, particularly those with asthma; and elderly people. Some results were available for subpopulations with preexisting disease, including cardiovascular disease patients. The number of these studies, however, was relatively small, and it was difficult to determine how robust the results were for specific susceptible subpopulations. Most research had focused on short-term exposures and largely acute morbidity responses and mortality, a few studies using time-series forms of analysis.

In toxicological studies using experimental animals, the focus before 1997 also had been on using high exposure concentrations or doses in young and healthy animals to evaluate responses primarily in the respiratory tract. Chronic high-dose exposure studies to carbon black particles or diesel exhaust, for example, were found to result in chronic inflammation to induce oxidative stress and lung tumors in rats. Significant species differences in such responses were seen related to species-specific defenses and

the persistence of the deposited PM. The focus almost exclusively was on the respiratory tract, and this tradition of using healthy animals, high exposure concentrations or doses and closely focusing on the respiratory system was unchanged in the first toxicological studies addressing the ambient PM issue. The use of compromised animal models was just starting, although they were rather crude and not much consideration was given for validation of the models or the issue of relevant doses.

General Populations

Before 1997, several studies had been completed on general populations, but data were not available across the typical life span. There were a few studies of infants and very few of PM effects on fetuses and newborns. Although awareness was growing that infant mortality might be linked to PM, less was known about less severe outcomes, such as lung function performance and the onset of asthma during the first few years of life. A few studies that were under way before 1997 were focused on pediatric health issues. Only a relatively small number of studies were available to address whether PM_{10} exposure was associated with acute respiratory health effects in healthy children. An even smaller body of science was available that addressed whether long-term exposure to high concentrations of air pollution in general and PM specifically had a negative effect on the development of lung function in children. Study-design limitations made distinguishing the relative impacts of O_3, NO_2, and PM difficult. Most of the studies that had been completed on health effects among adults and the elderly were for total populations, with a small number of studies distinguishing whether these individuals had preexisting diseases. Analyses of nationwide data sets indicated that mortality for these groups was related to PM concentrations, with indications that elderly people with cardiopulmonary disease were most affected.

Populations with Preexisting Disease

A larger body of studies existed before 1997 regarding the acute respiratory effects of PM on children with asthma as compared with studies on healthy children. The studies were generally consistent in finding an association of PM_{10} with asthma-related respiratory symptoms and related health outcomes. However, only a smaller subset of these studies included

multipollutant analysis, some studies finding adverse respiratory effects associated with other pollutants, such as O_3, as well as PM. Very few studies were available before 1997 indicating an association of PM and the development of asthma in children, although a small number of studies from outside the United States were suggestive of an effect on asthma prevalence from exposure to high concentrations of overall motor vehicle emissions (Wjst et al. 1993).

Adults and elderly persons who had been studied most often before 1997 were persons with preexisting disease (for example, cardiovascular or pulmonary diseases). Most of the studies used good design and analytic approaches, providing a sound foundation of knowledge indicating the importance of preexisting conditions.

The committee's first report pointed out the uncertainties associated with research on susceptible subpopulations. The committee expressed the hope that once refined dose estimates were made, epidemiological field studies could complete the framework for defining susceptible subpopulations. A number of additional shortcomings and gaps were listed in the committee's first report:

- Nature and severity of chronic adverse health outcomes have not been addressed.
- Short-term, peak, cumulative, and long-term exposures for long-term health effects.
- Chronic or life-shortening effects of PM in susceptible subpopulations.
- Extent of premature mortality attributable to acute PM exposure.
- Clinical and epidemiological studies to better define types and severity of PM-related health responses in susceptible subpopulations.

What Has Been Learned?

Since 1997, substantial progress has been made, and a number of publications have addressed the committee's concerns. In toxicology, efforts have been made to develop new animal models mimicking humans with compromised respiratory, cardiac, and vascular conditions, such as respiratory tract infection, allergic conditions, cardiac failure, and hypertension. Transgenic or knockout animal models have also been developed. However, more emphasis needs to be placed on the validation of these models to address the following issues: Are the mechanisms that cause a

certain compromised organ function and those that subsequently are responsible for PM-induced effects the same as those known to play a role in the respective human condition? Is an acutely induced disease to generate an animal model comparable to a chronic human condition? Similar questions can be asked when using transgenic and knockout animal models, and answers to such questions are important when extrapolating results from studies of compromised animals to susceptible human populations.

Perhaps even more important is the issue of relevance of administered doses; little attention is given to this issue in the published studies. Effects induced at 10- to 100-fold higher concentrations or doses might be caused by mechanisms that are different from those underlying low-dose responses. Toxicological studies are performed at several dose levels so that dose-response relationships can be established, and the shape of this relationship (linear or nonlinear) can be used for defining and interpreting effects of relevant doses.

A few toxicological studies have focused on the impact of age as a susceptibility factor by using aged rats and mice. Exposures by inhalation of laboratory-generated particles of different composition and of concentrated ambient particles have been performed, with and without sensitizing the animals to mimic respiratory inflammatory or vascular hypertensive conditions. A promising tool for analyzing age-related differences is the approach by one group to compare in vitro the effects of different particle types on initiating cellular and molecular responses. The result of age-related differences still being discernable in vitro needs to be exploited in future studies to obtain more information on mechanisms leading to increased susceptibility.

About 30 epidemiological projects that address some aspect of susceptible subpopulations' risks from PM exposures have been completed. The larger number of completed studies has been on children age 1-17, both healthy children and those with asthma, and elderly persons. Most studies have focused on short-term effects (for example, lung function performance, cardiac arrhythmia, and exacerbation of asthma) or mortality. Most of the completed projects on children have been conducted outside of the United States.

Around 100 epidemiological projects are ongoing with completion dates in the next few years. About half of the projects on children are being conducted in the United States, the remainder being primarily in Europe.

Considerable progress has been made in clinical and epidemiological cohort studies in susceptible populations. To address the question of whether changes in particle deposition contribute to increased susceptibility,

studies of people with asthma or COPD have been performed, and more are being initiated to determine the differences between healthy people and those people with respect to the deposition of differently sized inhaled particles in the respiratory tract. Other clinical studies have examined parameters of respiratory, vascular, and cardiac outcomes following exposure to laboratory-generated ultrafine particles and to diesel exhaust. Only three or four research groups in the United States and Europe are involved in controlled clinical studies using compromised subjects.

Epidemiological studies using cohorts of COPD and chronic artery disease (CAD) patients with personal EKG monitors have been initiated. The studies include measurements of respiratory and vascular parameters. Significant effects on blood parameters, associated with either $PM_{2.5}$ or ultrafine particle concentrations, have been observed in CAD patients (A. Peters et al. 2001a,b; Ibald-Mulli et al. 2002; Pekkanen et al. 2002).

Overall, the numerous epidemiological studies have been of high quality, accounting for many co-exposures and potential confounders. The studies have also addressed sources of bias and other research design and measurement issues that affect the interpretation and validity of the results. The body of epidemiological evidence is growing in support of the hypothesis that certain subpopulations, by virtue of their age and preexisting disease status, are more susceptible to adverse health effects from PM exposures. The specific component or size of PM responsible for these effects is less clear.

General Populations

One of the key findings since 1997 is the identification of acute health effects in persons not known to have preexisting disease. These effects have been observed at low concentrations of PM exposure, as described below. There is one design issue, however, that limits interpretation of much of the available epidemiological data to answer questions about susceptible subpopulations. Many of these studies have included data for populations that include newborns through elderly persons. When data are presented for children, they are typically grouped as 0-14-year-olds, thus merging data for individuals in very different stages of physiological development (Snodgrass 1992; Mennella and Beauchamp 1992; Burri 1997; Pinkerton and Joad 2000; Mathieu-Nolf 2002). Conclusions specific to largely homogeneous subpopulations (such as infants or elderly persons by birth cohort) cannot be drawn from much of the epidemiological literature.

In addition, many epidemiological studies do not indicate whether the populations studied included persons with or without preexisting conditions. When authors do not identify whether they studied persons with such conditions, the presumption is usually made that the individuals are representative of the general population. Consequently, the findings for general populations compiled here follow that convention.

Fetuses and Newborns

During the past 6 years, a few new epidemiological studies on fetal or newborn health outcomes were published. However, the evidence remains limited, and the uncertainties are large.

Birth weight and intrauterine growth rate (IUGR) are the two most common measures used to look for PM or gaseous air-pollutant-related health effects in this subpopulation. Decrements in both health measures have been quantitatively linked to increases in PM. IUGR has been significantly related to TSP and maternal exposures to c-PAH in the first month of pregnancy, when other factors were taken into account (Pereira et al. 1998). Very low birth weight has been linked to increased levels of TSP and SO_2 in the first and third trimesters of pregnancy (Rogers et al. 2000). These results merit further investigation.

Other outcomes studied included prematurity, cardiac and orofacial defects, intrauterine and infant mortality and stillbirth. Prematurity and premature mortality have been significantly related to first trimester maternal exposures to TSP (Bobak and Leon. 1999). A borderline significant association has been reported for PM_{10}, especially nonsulfate PM_{10} (sulfate results were negative and highly significant), and sudden infant death syndrome (Lipfert et al. 2000b), consistent with the PM_{10} findings of Woodruff et al. 1997. Intrauterine mortality, stillbirths, and cardiac and orofacial defects have not been significantly correlated with PM_{10}.

Pregnant Women

Very few studies have examined the health effects of PM and other air pollutants in pregnant women. That might be due in part to the lack of viable hypotheses that have been conceptualized to date. Hypertension and diabetes are the two most commonly documented complications of pregnancy (Alessandri et al. 1992; Fretts and Usher 1997). In 1998, diabetes

alone affected over 100,000 pregnancies and 2.6% of all live births in the United States (Ventura et al. 2000). The seriousness of the adverse maternal and fetal effects and the extent of related medical costs increase with the severity of the mother's diabetic and/or hypertensive condition (e.g., Hanson and Persson 1993; Meis et al. 1998; Sibai et al. 1998, 2000). Medical interventions include medications for diabetic pregnant women, and restricted activity and smoking cessation for hypertensive women (Cunningham et al. 2001). With the new cardiovascular results and findings about diabetics (for example, Goldberg et al. 2000; Zanobetti and Schwartz 2001), it may be time to consider whether pregnant women, particularly those with diabetes and/or hypertension, and their fetuses are at even greater risk of adverse health effects when the women are exposed to PM. Investigators who have access to data from completed studies involving pregnant women may be able to reanalyze their data with the new cardiac evidence in mind. New studies may need to be designed so that knowledge can be developed about PM impacts on women during their pregnancies.

Infants (1 Month to 1 Year of Age)

Over 10 new epidemiological studies in the period 1998-2002 have presented data separately for children less than 1 year of age. The quality of these studies has been good; the authors have taken care to gather extensive data, evaluate the potential impacts of cofactors and confounders, and discuss the limitations of their investigations. Some studies have benefited from individual-level data, allowing for control of potential personal confounders in their analyses. In most cases, however, aggregated clinical, hospital, or population-scale data have been used to study infant health impacts.

The health measures most often used have been indicators of respiratory function, hospitalization and infant mortality (all, respiratory, nonrespiratory, and sudden infant death syndrome). Studies using different study designs (matched case-control, time series, and cohort methods) have found significant associations between PM and infant mortality. For example, Loomis et al. (1999) conducted a time-series analysis and quantified significant relationships between excess infant mortality and mean concentrations of ambient fine $PM_{2.5}$, NO_2, and O_3 3-5 days before death. The association of $PM_{2.5}$ and infant mortality is the most consistent finding for this subpopulation. The evidence is weaker and less consistent, however, for relationships between PM and less severe health outcomes.

Children (1-17 Years of Age)

Several new studies have been published with mixed results, with more studies finding effects on dry cough, nonasthma respiratory symptoms, physician visits, hospital admissions, and emergency department (ED) visits. Most studies used PM_{10} and a smaller subset included $PM_{2.5}$ as the pollutant indicator with several also examining one or more copollutants. There has been a substantial increase in the number of studies since 1996; however, the evidence is strongly suggestive but not yet unequivocal regarding the impact of PM on respiratory symptoms and related health outcomes in healthy children. The relative impact of the contributions from other pollutants (for example, O_3) to respiratory symptoms and related health outcomes also remains uncertain. The inconsistencies in the results from these studies may be a result of their small sample sizes and limited statistical power. Additionally, aggregation of children across developmental stages may have reduced the investigators' abilities to detect adverse health effects (Snodgrass 1992; Mennella and Beauchamp 1992; Burri 1997; Pinkerton and Joad 2000; Mathieu-Nolf, 2002).

Since well-designed longitudinal studies are expensive and difficult to sustain, the small number of published results for lung function development from studies since 1997 is not unexpected. A well-designed study for this outcome (J.M. Peters et. al. 1999a,b) is indicative of a relatively small but significant negative impact of PM on long-term lung development in children. The limited number of other published studies on this health outcome generally supports these findings. The significance of the contribution of NO_2 to these findings remains uncertain, though NO_2 may be a marker of motor vehicle air pollution.

Several studies have used motor vehicle traffic source category, which included PM, as the pollutant indicator. Studies have generally been consistent in finding association with relatively close proximity (less than 200 m) to major traffic sources and adverse health outcomes in children, especially for asthma-related outcomes.

Adults (18-64 Years of Age)

Epidemiological evidence published in the past 5 years has confirmed many of the earlier findings for adults. An increasing number of publications have reported the results of investigations into the relationships between PM (ultrafine, fine, $PM_{2.5}$, PM_{10}, and coarse PM), gaseous pollut-

ants, and a range of health outcomes (for example, lung-function measures, ED and hospital visits, cancer incidence, and mortality). Panels, diary studies, cohort, case cross-over, and time-series methods have been used, and in many cases, great care was taken to examine the impacts of copollutants, cofactors, confounders, and sources of bias. The results of these studies are generally consistent, the most significant risk ratios for morbidity being between 1.0 and 1.4 per 50 $\mu g/m^3$ increase in PM_{10} or 25 $\mu g/m^3$ increase in $PM_{2.5}$. Mortality studies have generally found risk ratios of 1.01 to 1.06 for similar increments of $PM_{2.5}$. Although the quality of the evidence has been strong, inconsistencies in the results indicate that uncertainties remain. Much has been learned that is of scientific value, but not all of the needed information is available to make policy decisions. There are studies in progress that can be expected to address these issues.

There have been and continue to be very few epidemiological studies that have examined and reported air pollution impacts on minority populations. Major uncertainties remain about minority subpopulation risks of PM-related adverse health effects. Although data about minorities may be available in many studies, very few researchers have reported or even discussed the limitations of their data on racial or ethnic groups. It may be appropriate to consider whether a reanalysis or meta-analysis of existing large databases is timely. Socioeconomic status has predominantly been used as a factor in analyses to account for potential confounding related to life style and health-care practices. This approach is not likely to be an adequate surrogate for the complex of factors that contribute to minority health responses to air pollution exposures.

Elderly Persons (65 Years of Age and Older)

A rapidly growing body of epidemiological literature focuses on the air-pollution-related health risks to elderly people. Compared with the studies available 6 years ago, the evidence is stronger and more consistent for important health responses in this sensitive subpopulation. Although some uncertainties have been reduced, the studies now available have increased scientific knowledge about this subpopulation's risks and generated new information for policymakers. The continuing research in this area can be expected to contribute additional quantitative results that will enhance abilities to explain the current discrepancies and to develop policies.

Some important gains in knowledge have been made about this

subpopulation. Several studies, including ones that have used appropriate techniques to control potential confounders and time-series analyses, have reported that healthy elderly persons are adversely affected by air pollution. For example, Samet et al (2000b) showed that hospital admissions increase in conjunction with increasing concentrations of PM_{10}. In additional studies, measures of pulmonary function and blood pressure, daily hospital visits, and mortality have been used to examine the impacts of air pollution on the elderly. Studies of heart-rate variability have linked decreased variability with increasing cases of CAPs (involving $PM_{2.5}$) (for example, Creason et al. 2001), but studies of other acute health measures (such as lung-function measures) and PM have resulted in nonsignificant correlations (see Berglund et al. 1999). The data on daily ED visits, hospitalizations, and mortality are inconsistent. For example, one study found no strong relationship between air pollution and ED visits for respiratory conditions (Rosas et al. 1998), but another reported that $PM_{2.5}$ concentrations on the previous day were associated with ED visits but were confounded by temperature and O_3 concentrations (Delfino et al. 1998). Studies that have linked PM (PM_{10} and coarse) levels to daily mortality among the elderly have typically reported weak or borderline significant associations (Mar et al. 2000; Gouveia and Fletcher 2000; Sanhueza et al. 1998). Heart-rate variability has also been linked to $PM_{2.5}$ exposure concentrations (Devlin et al. 2003). The impacts of measurement and modeling choices on the findings have not been fully explored.

Populations with Preexisting Disease

Persons with health conditions that compromise their overall health are often more responsive to air pollutants. Knowledge gained in the past 6 years has deepened that recognition and added substantial and coherent evidence that is of value both to scientists and policymakers.

Lung Diseases

Children with Asthma. The number of studies done since 1997 has increased considerably. The overall findings generally show an association between respiratory symptoms in pediatric patients with asthma and PM-, especially $PM_{2.5}$-, related health outcomes (for example, medication use, hospital admissions and ED visits, and lung function). Studies indicate an

impact of PM independent of other copollutants, although other pollutants (such as O_3 and acids) also might affect these outcomes.

A small number of studies since 1997 suggest a potential association between $PM_{2.5}$ or PM_{10} and the development of asthma (for example, Gehring et al. 2002). The contribution of copollutants is unclear, as the majority of studies used source categories (such as motor vehicle traffic) as pollutant indicators. This health outcome requires substantial additional investigation.

Adults with Asthma. Several studies show increased risk of asthma-related ED visits and hospitalization associated with PM_{10}, and a few studies link hospitalization with $PM_{2.5}$ (Lipsett et al. 1997; Burnett et al. 1999; Sheppard et al. 1999; Tolbert et al. 2000b). However, total suspended particulates have been significantly related to exacerbations of asthma, including increased cough, phlegm, wheeze, and persistent cough and phlegm. Another indicator of health impacts has been increased use of bronchodilators. Significant associations of ultrafine and fine particles, and PM_{10} with lung-function measures and shortness of breath have been reported in several studies, findings that are consistent with those in the early 1990s. Adults with asthma also experience increased airway resistance and hyperresponsiveness when exposed to diesel exhaust (Nordenhall et al. 2001). Adverse health effects in asthma patients from lung-function deficits, respiratory symptoms, ED visits, or mortality have all been positively related to PM, either PM_{10} or TSP.

Adults with Chronic Obstructive Pulmonary Disease. The strength of the evidence for the association of adverse health effects with PM and other air pollutants is increasing for this susceptible subpopulation. Acute symptoms, ED visits, and mortality have been examined in numerous new studies. The results have often been consistent, particularly for mortality. Several studies have reported that after adjusting for potential confounders and cofactors, PM_{10} was related to daily morality for all, respiratory, and cardiovascular causes. Various studies have related PM_{10} and $PM_{2.5}$ concentrations to hospitalization and acute health effects, such as lung-function measures. Clearly, persons with respiratory conditions are at greater risk for adverse health responses than the general population.

Elderly Persons with Chronic Obstructive Pulmonary Disease. Several studies have focused on this vulnerable subset. The research to date has primarily used mortality measures to examine air pollution impacts. Daily rates of all-cause, respiratory cause, and specific causes of mortality have been studied. When Goldberg et al. (2000) used a 3-day lag analysis, PM_{10} was significantly related to daily mortality for all causes and COPD.

When primary and underlying causes of death were considered, PM_{10} was significantly related to respiratory mortality. When medication use and presence in a medical care unit were considered, these mortality risks were reduced. An increase in excess respiratory deaths appears to be due to air pollution, but the results to date have not been entirely consistent. $PM_{2.5}$ has been associated with acute lower respiratory disease, congestive heart failure, cardiovascular disease, and heart-rate variability.

These findings come from time series analyses of large, population-scale data sets. The evidence contains some inconsistencies, but the trends indicate that this subpopulation is one of concern.

Cardiovascular Diseases

Adults with Cardiovascular Disease (CVD). There is less information on the health risks presented to this subpopulation by air pollution. In one study, adults with cardiac diagnoses were found to have dysrhythmia rates positively associated with all measures of PM (Stieb et al. 2000). Daily respiratory and cardiovascular mortality and ED visits among these patients were linked to PM as well.

Elderly Persons with Cardiovascular Disease. The largest number of studies of the elderly has focused on this particular subset. Daily mortality due to CVD causes has been linked significantly to PM_{10}. Hospitalizations for CVD and cerebrovascular conditions have been significantly related to daily measures of PM_{10}. However, these results have not been consistent across all geographic areas studied.

Acute measures such as daily pulse rates, blood oxygen saturation, and hemoglobin changes have been related to PM_{10} concentrations when other factors have been controlled, but the relationships have not always been significant or consistent. Heart-rate variability, acute lower respiratory disease, congestive heart failure, and cardiovascular disease in this sensitive subpopulation have been linked to $PM_{2.5}$ (Goldberg et al. 2000).

Exacerbations of CVD have been noted in several studies, but it is difficult to attribute the effects specifically to PM. For example, acute respiratory infections and PM exposures together have been found to worsen underlying cardiac disease, resulting in increased hospitalization rates (Zanobetti et al. 2000). However, knowledge about the combined effects of pollution and infection is incomplete at this time.

Several studies in different parts of the world have linked PM_{10} to more serious health-outcome measures, such as daily hospitalization and

mortality (all, CVD, and respiratory causes), but some of these associations have been weaker than others. One study reports little evidence of heterogeneity across U.S. cities for the relationship between daily variations in PM_{10} and hospitalization for heart disease (Schwartz 1997). Studies of elderly persons with preexisting CVD have not shown significant associations between PM and clinic or ED visits. Research by Goldberg et al. (2000) suggests that a wider range of health outcomes in persons with preexisting conditions and the impacts of their use of medications to control those conditions need to be considered when evaluating the health impacts of PM.

These results have been obtained from studies that used time-series, panel, and cohort research methods. Many of these investigations accounted for the impacts of gaseous pollutants and other potential confounders when conducting the analyses. Many of the research teams described the strengths and limitations of their methods, data, and analyses; particular attention was directed at the potential impacts of exposure and outcome misclassification. Many of the studies also provided sufficient quantitative information to determine the unit change in health response in correspondence to the unit change in exposure.

Persons with Hypertension. Goldberg et al. (2001) found no association between hypertension and mortality and PM concentrations. In their study of veterans' health, Lipfert et al. (2000a) linked PM exposures and blood pressure. These results merit further investigation.

Diabetes

The first identification of diabetes as a potential disease of a susceptible subpopulation was reported by Goldberg et al. (2000). They found that the mortality from diabetes was correlated consistently and significantly across all PM metrics. More recently, diabetic patients were found to have higher rates of hospitalization for heart disease, but not lung disease, in relationship to PM_{10} exposures. Pneumonia was also an effect modifier for the younger persons with diabetes, and COPD was the modifier for older persons with diabetes. The authors concluded that people with diabetes are a susceptible subpopulation for PM exposure (Zanobetti and Schwartz 2001).

Other Issues

Some progress has been made in other areas (for example, the impact of peak, cumulative, and long-term exposures), but additional work remains to be done to address important uncertainties. Questions remain about the impacts of chronic PM exposures, the extent of people dying prematurely, which people are dying, and the nature of adverse health effects among ill adults and pregnant women.

Socioeconomic status has also been shown to modify the association between particulate air pollution and mortality. Krewski et al. (2000) showed that mortality associated with long-term exposure to particulate air pollution decreases with increasing educational attainment. Limited evidence of a similar modifying effect of socioeconomic status has also been shown in time series studies of air pollution and mortality (Villeneuve et al. 2003).

Overall, there is a need for more research on susceptible subpopulations and a need for more animal (models and defining mechanisms), clinical, cohort, and chronic health-effects studies.

Synthesis

From 1998 to 2002, nearly 200 epidemiological reports on susceptible subpopulations have been published. Well over 100 of those reports have been on healthy and asthmatic children ages 1-17. Among the studies, most used PM_{10} data, while less than 15% analyzed exposure to $PM_{2.5}$. The second largest set of epidemiological publications has been on the adults with preexisting conditions.

About 30 reports on the topic of susceptibility in toxicology have been published, a peak of 15 appearing in 2000. As pointed out previously, animal models are still not well validated, and doses used are consistently high to very high. Although useful for forming hypotheses or for indicating a specific mechanistic concept, the results need to be verified with realistic dose amounts. The major research results include the following new findings:

- Studies in rodents show that the aged are more susceptible and that infection is an additional risk factor.

- Toxicological studies in dogs and rodents show impacts of PM on cardiac physiology and vascular parameters.
- Asthma and COPD patients deposit greater amounts of inhaled fine and ultrafine PM.
- Cardiac physiological changes in the elderly are induced by PM exposures.
- Hematological factors, such as blood coagulation and acute phase proteins, change after PM exposure.
- Maternal PM exposures may result in reduced intrauterine growth rates, permaturity, and low birth weight among newborns.
- Patients with diabetes are at greater risk, probably related to their compromised cardiovascular condition.

The major research results also include support for earlier findings:

- PM-induced cardiovascular and respiratory effects show associations with PM measures in many new studies.
- More studies show health effects in children; exacerbation of preexisting illness in children with asthma.
- In the elderly, acute respiratory infection adds to cardiovascular effects following PM exposures.

Results from epidemiological, clinical, and animal studies are converging around the hypothesis that PM exposures result in cardiovascular changes. Both fine and ultrafine particles have been found to induce respective effects. Uncertainty remains, however, about the impact of copollutants. It is becoming more obvious from clinical and toxicological studies that ambient fine PM induces respiratory and cardiovascular events that in susceptible, compromised people can explain the morbidity and mortality observed in epidemiological studies. Parts of mechanistic sequences of effects that have been proposed are revealed and appear to explain PM effects observed in susceptible subpopulations.

Although the body of epidemiological evidence is growing in support of the hypothesis that certain subpopulations, by virtue of their age and/or preexisting disease status, are more susceptible to adverse health effects from PM exposures, the specific component or size of PM responsible for these effects is less clear. Consistent associations have been found for ultrafine, fine, and PM_{10} levels with lung-function performance in asthmatic adults, and for proximity to traffic for asthmatic and healthy children. Similarly consistent are the associations of PM_{10} and mortality among adults

with preexisting COPD. Less consistent relationships have been found for PM and lung-function measures for infants; daily ED visits, hospitalizations, and mortality among adults; excess deaths among elderly persons with COPD; and hospitalization rates and acute health measures in elderly persons with CVD.

Some improvements in synthesis and communications have occurred among scientists in different fields who are working to identify susceptible subpopulations. In the past 6 years, the EPA-funded PM centers were established with a mandate to foster communication, and the envisioned interdisciplinary cross-fertilization has been occurring. The NRC committee held a workshop on susceptible subpopulations to convene epidemiologists and toxicologists who were working on this issue and to foster interdisciplinary synthesis of research results. The committee's concern is that without explicit support of communication across disciplines, such synthesis will be difficult to sustain.

Scientific Value

Given that there were about 3.5 million hospital discharges for respiratory disease and about 4.2 million hospital discharges for heart disease in the United States (EPA 2002a), the effect of PM is large, even if only a small percentage of the hospitalizations is associated with PM exposure. Therefore, knowing more about specific characteristics of host-environment interactions with PM would be of high scientific and societal value. A better understanding of how PM of different size fractions causes adverse effects in susceptible subpopulations will allow a focused approach for remedial measures.

Decisionmaking Value

With improved knowledge about susceptible subpopulations and the impact that specific sizes of PM have, individuals of these groups could be better protected by appropriate standards. There is little new information about susceptible subpopulations, however, to inform decisions about PM indicators. There is still inadequate dose-response information about ultrafine PM and effects in susceptible subpopulations; filling this gap will be highly valuable for decisionmakers.

Information Expected in the Near Future

A limited number of ongoing, long-term epidemiological studies are expected to provide information on the health effects of air pollution, including PM. The Southern California children's study may provide additional information on the relationship of air pollution to lung-function development in children. Ongoing studies of children in Europe may also provide information on the contribution of air pollution to the development of asthma in children. The Harvard Six Cities Study (Dockery et al. 1993) and the American Cancer Society's Cancer Prevention Study 2 (Pope et al. 1995) may provide additional information on the relationship of air pollution to cause-specific mortality in older populations. Other studies are under way to examine and potentially confirm the relationship between maternal PM exposures and impacts on fetal growth and birth weight, and between early childhood PM exposures and health outcomes. These studies are being conducted in the United States and in Europe.

Similarly, many animal studies in progress can be expected to yield valuable insights and data. Studies are widening with repeated exposures of rodents to ambient particles, either with CAPs using a mouse model of endothelial dysfunction or with PM next to or on highways using rat models of old age and preexisting inflammation or hypertension.

Animal studies mimicking cardiovascular conditions are under way to investigate mechanistic events using toxicogenomic and proteomic analyses. In vitro studies exposing primary cells from young and old rodents to PM are finding significant differences between age groups with respect to expression of preinflammatory cytokines and antioxidant cleft proteins. As an understanding advances about PM concentrations and the related doses received in the respiratory tract, researchers will be better equipped to interpret associated adverse health effects in susceptible people. Other studies are under way to investigate whether air pollution has effects on the central nervous system (CNS); these include comparative studies of histological changes in brains of dogs from a highly polluted area versus a less polluted area. Still other studies are exploring the translocation of inhaled ultrafine particles into the brain of rats. The results of these studies may provide insights relevant to susceptible subpopulations.

Major Remaining Uncertainties

Several major uncertainties need to be addressed for susceptible subpopulations. One key remaining area is whether chronic exposure to

ambient PM is associated with the development of disease (for example, asthma and lung cancer) and organ dysfunction (for example, diminished lung function). Although there is some evidence from a small number of studies for associations between chronic exposure to PM and those health effects, further information on the magnitude and scope of those important public health outcomes is necessary.

A number of studies have found an association between exposure to PM and premature death, especially in the elderly with existing cardiopulmonary disease. The current body of scientific evidence suggests that the amount of life-shortening from exposure to PM is not limited to advancing death by a matter of days in those already severely ill ("harvesting"), but includes a longer-term phenomenon involving advancing death by months or even years. However, further refinement of the extent of life-shortening from PM remains an area requiring additional research.

The largest fraction of the smaller ultrafine particle sizes consists of organic carbon compounds. In vitro studies with lung cells have found that some of these compounds cause oxidative stress. Therefore, there is a need to investigate the potential of these particles to cause adverse health effects in vivo. Because of the increased deposition of inhaled ultrafine particles in the respiratory tract of susceptible people (asthma and COPD patients), greater effects in this group compared with healthy people would be expected. This issue needs to be examined.

One mechanism by which PM, specifically ultrafine particles, might cause extrapulmonary effects is through their translocation into the circulatory system and subsequent distribution throughout the body. The CNS is a potential target organ, and both acute and long-term effects could be postulated if these particles reach the CNS. Both endothelial effects (endothelial dysfunction) and altered neuronal functions in brain regions could result. Thus, studies to determine the potential of PM (or subfractions of it) to have long-term and acute effects on the CNS in both healthy and susceptible people are needed.

Most epidemiological studies report findings for entire populations or for large, aggregated groups (for example, children, elderly persons, persons with preexisting disease). Such results do not advance knowledge about largely homogeneous susceptible subpopulations (for example, infants, young children (1-4 years old), and adults, and elderly persons). Similarly, broad disease categories (such as cardiovascular disease) might mask important subpopulations. Epidemiological studies of specific age and disease groups are challenging, but existing studies might have data that can be reanalyzed or can contribute to meta-analyses to shed new light on subpopulations' responses to PM exposures. Regardless, researchers should

comment on the ability or limitations of their studies to address susceptible subpopulation issues. More thorough consideration of susceptible subpopulation issues during the design, analysis, and reporting of epidemiological studies is needed. Uncertainties about effects of PM on specific subpopulations cannot be addressed without findings reported for more homogeneous subpopulations.

Mechanisms by which PM causes effects in susceptible people with compromised organ functions can differ from mechanisms in healthy subjects. However, specific mechanisms causing altered organ functions, whether in healthy or in compromised individuals, are possibly the same, and the dose only needs to be higher in the healthy organism to cause similar adverse effects as those seen in susceptible people. Therefore, it would be valuable to obtain more information about cellular and molecular mechanisms of PM effects for both groups. That information would greatly help in the design of future studies with respect to administering high and very high doses when using healthy animals to study PM effects.

By far most toxicological studies on the effects of PM have been performed using young, healthy animals. Consequently, very high doses were used to see PM-related effects. As pointed out, underlying mechanisms in the healthy organism may be very different from the compromised organism. In addition, animal models of a specific human disease or condition may reflect only one aspect of the human disease state and may not be relevant for others. For example, rodent models of asthma using ovalbumin-sensitized mice are in some respect similar to the human condition by showing inflammatory airway responses upon allergen challenge, but they lack the bronchial constrictive response. In the model of spontaneously hypertensive rats, hypertension is due to pathophysiological mechanisms that are also different from the human condition. Another example is monocrotaline-induced pulmonary hypertension, resulting in an acute, highly destructive pulmonary inflammatory condition that is very different from the slow-developing human disease. Thus, the relevance of a chosen animal model for mimicking a human compromised organ function needs to be validated by identifying mechanistic pathways to identify similarities and differences between the human disease and the animal model.

Results of PM monitoring are usually expressed as 24-hr averages. Any shorter exposures or excursions occurring during the day are thereby averaged out and are not recorded. However, short-term and peak exposures may be important dose modifiers with the potential to induce adverse effects in susceptible subpopulations. Knowledge about short-term and peak exposures during a 24-hr monitoring period is needed to be able to correlate responses observed in susceptibles with such exposures. This

knowledge would allow an evaluation of the importance of short-term and peak versus average PM exposures and effects.

What Remains To Be Done?

Despite the recent advances in knowledge, substantial uncertainties about susceptible subpopulations still need to be addressed. These uncertainties require development of new knowledge and improvement of research methods.

To create the knowledge needed to understand the impacts of PM on susceptible subpopulations, research should more effectively address different scales of exposure (from short-term, peak, to chronic exposures), characteristics of exposure (such as deposition and disposition of fine and ultrafine particles in the respiratory tract), cellular and molecular mechanisms, the range of potential adverse health effects (such as development of disease and organ dysfunction, neurotoxic and extrapulmonary effects, and life-shortening), and potential effect modifiers (such as preexisting disease, including infections). Current concerns focus on whether chronic PM exposures relate to the development of disease and organ dysfunction, the extent to which ultrafine particles of about 20 nanometers (nm) in size induce adverse effects in asthma and COPD patients, and the magnitude of life-shortening from PM exposures.

In addition, study methods should be improved. Important needs are the validation of animal models and demonstration of the relevance of these models, especially for mimicking compromised organ functions found in susceptible human subpopulations. In epidemiological studies, cohorts investigated often include individuals at very different points of physiological development (such as children ages 0-14) or with a wide range of health conditions (especially adults over age 65). Although such aggregation may make a study more manageable or improve statistical power, opportunities to examine adverse health effects among specific subpopulations are lost. Some researchers indicated that they collected data on children, for example, but did not describe, analyze, or comment on those data sufficiently for readers to gain any new knowledge or hypotheses about pediatric health concerns. With the number of large-scale studies now available, it may be possible to combine and analyze data for key subpopulations using meta-analysis or other techniques, thereby, capturing insights that might otherwise be lost.

RESEARCH TOPIC 9
MECHANISMS OF INJURY

What are the underlying mechanisms (local pulmonary and systemic) that can explain the epidemiological findings of mortality and morbidity associated with exposure to ambient particulate matter?

Introduction

The need for the 1997 PM_{10} and $PM_{2.5}$ NAAQS came primarily from a large and coherent epidemiological database showing significant associations between ambient air PM concentrations and excess mortality and morbidity. Although the 1996 criteria document provided some support for biological plausibility of causal links between PM exposure and health effects, mechanistic evidence from controlled human and animal exposure studies and other approaches was largely unavailable. One of the major advances in PM research over the past few years is the identification of several plausible biological mechanisms that are consistent with the epidemiological findings. Many of the mechanistic findings resulted from controlled exposure and in vitro studies using particles comparable to or derived from those found in ambient air (both concentrated or filter-collected ambient particles and laboratory surrogate particles) and from studies in animal models and human populations susceptible to the effects of PM.

Recently, several mechanistic pathways have been investigated that might underlie the link between PM exposure and adverse health effects. Figure C-2 highlights the complexity and interdependency of some of these pathways (Lippmann et al. 2003). The portal of entry for PM air pollution is the lungs, and PM interactions with respiratory epithelium probably mediate a wide range of effects, as indicated by the central oval in Figure C-3. These effects include respiratory as well as systemic and cardiovascular effects taking place via different mechanistic pathways. For example, PM, or its reaction products, might stimulate airway sensory nerves, resulting in changes in lung function and in autonomic tone, which influences cardiac function. Ultrafine particles, by virtue of their extremely small size, might enter pulmonary capillary blood and be rapidly transported to extrapulmonary tissues, such as liver, bone marrow, and heart, with either direct or indirect effects on organ function (Oberdorster and Utell 2002).

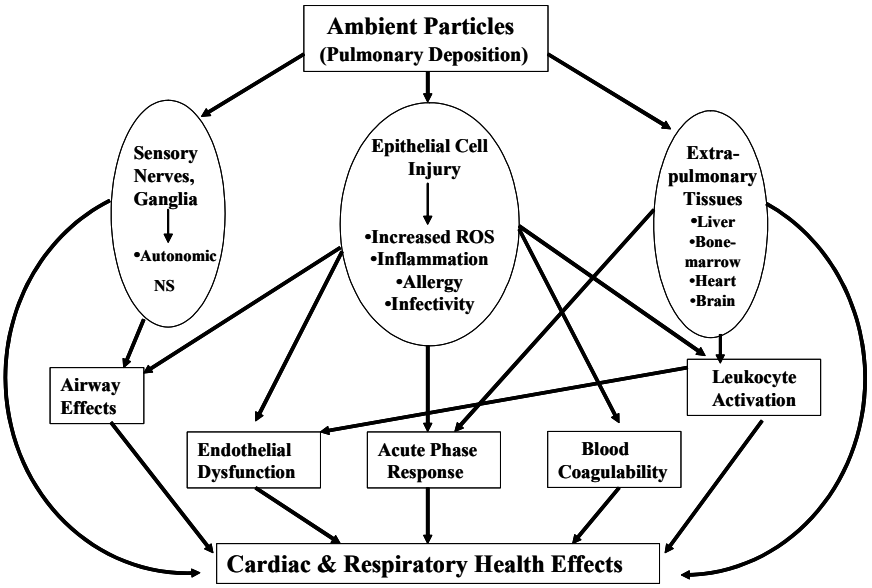

FIGURE C-2 Biological mechanisms of PM: from exposure to effects.

Recent findings demonstrate several pathways by which particles can affect the respiratory tract and cardiovascular systems: the induction of inflammatory responses in the lungs; the induction of systemic inflammatory and other vascular responses; and changes in neuronal control of heart function (HEI 2002b; Oberdorster et al. 2002; Lippmann et al. 2003). Thus, deposition of particles in the airway can induce effects in both the lungs and throughout the body (systemically) that might result in adverse effects in the exposed individual.

State of Understanding in 1997

At the time of the initial report, there were few mechanistic data to support the epidemiological findings of increased mortality and morbidity. The emphasis up until that time was on sophisticated pulmonary mechanics and pulmonary defense mechanisms, such as mucociliary clearance rates. The materials investigated were primarily secondary inorganic aerosols, including nitrates and sulfates, with a few studies addressing carcinogenicity of diesel exhaust. The responses were found to be largely negative

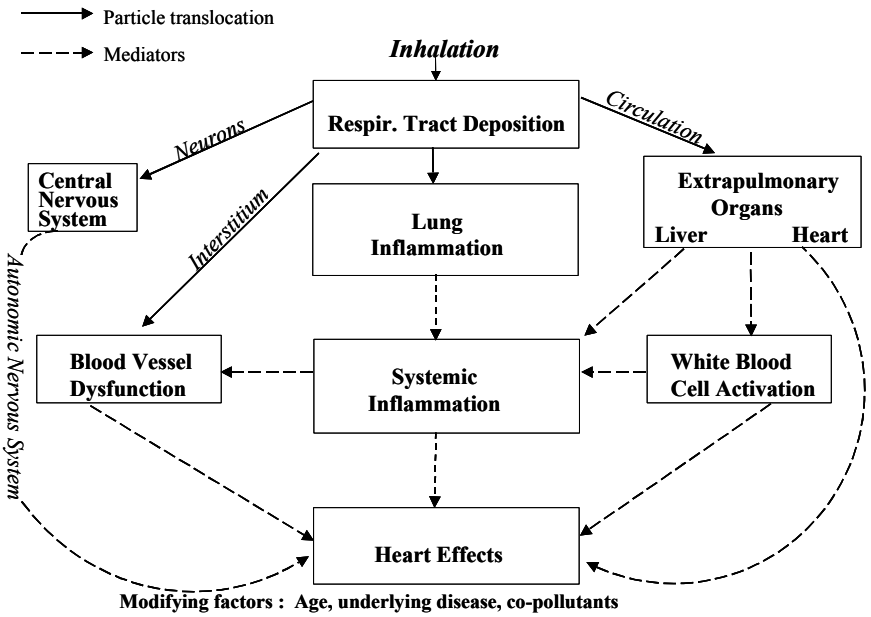

FIGURE C-3 Suggested mechanisms of PM particle effects.

except at high concentrations and with some suggestion of increased susceptibility of adolescents with asthma (Koenig et al. 1983). In addition, given the findings from the epidemiological studies of emerging increased risk for cardiovascular effects of PM exposure, there was a paucitiy of toxicological studies looking at possible mechanisms. Firmer conclusions for policy implications appeared to be dependent on finding underlying mechanisms that would explain why cardiac effects could be anticipated. In essence, the findings from the epidemiological studies were brought into question because there was essentially no supporting toxicological or physiological mechanistic evidence. For the most part, the findings were questioned not because there were data to refute the hypotheses but mostly because cardiopulmonary health effects of pollutant exposure had simply not been explored.

In response to the lack of a mechanistic underpinning in support of the epidemiological findings, the committee called for an ambitious agenda of carefully designed mechanistically based controlled exposure studies. Interest was expressed in understanding the level of damage to pulmonary

tissue itself and, on the cellular and molecular level, to better identify the causal pathway whereby resultant cardiorespiratory morbidity and mortality could be obtained following particle deposition in the lungs.

Several categories of studies were requested using three approaches:

- Controlled clinical studies.
- Animal toxicological studies.
- In vitro studies.

What Has Been Learned?

A major gain in mechanistic understanding since 1997 involves an expansion in focus to cardiovascular and subtle pulmonary responses. For the first time, investigators have considered the lung as a portal of entry rather than simply a target organ for PM. A workshop in March 2001 brought together epidemiologists, cardiologists, and toxicologists from academia, government, and industry to discuss potential mechanisms of cardiovascular effects from inhaled PM (Utell et al. 2002). On the basis of epidemiological and experimental data, workshop participants suggested that mechanistic considerations should focus on alterations in the autonomic nervous system; ischemic responses in the myocardium; chemical effects on ion channel function in myocardial cells; and inflammatory responses triggering endothelial dysfunction, atherosclerosis, and thrombosis. The hypothetical pathways involved are depicted in Figure C-3 along with some of the potential measurable mediators (Utell et al. 2002). The workshop further emphasized that a large armamentarium of tests is available to assess specific mechanistic pathways underlying the cardiovascular effects of air pollution whether investigating autonomic control of the cardiovascular system; myocardial substrate and vulnerability; or endothelial function, atherosclerosis, and thrombosis. In fact, recent studies in humans and animals have demonstrated alterations in the autonomic nervous system, cardiac repolarization, and endothelial responses in response to particles. A second workshop in Spring 2002 jointly sponsored by the National Institute of Environmental Health Sciences and EPA on environment and cardiovascular disease explored potential basic and clinical mechanisms as the basis for a research agenda. Significant advances were made in studies using dogs and rodents with regard to cardiovascular outcomes. Descriptive findings of EKG changes and vascular outcomes confirmed a role of ambient PM and surrogate particles on extrapulmonary organ functions. As a basic

mechanism for these effects, local and systemic oxidative stress responses were identified, as was a central role of oxidative stress in in vitro models.

Together with the shift in mechanistic focus, there were appreciable changes in the experimental systems used. For example, animal models used in recent years have changed appreciably from those used in the past. More emphasis has been given to potentially susceptible animals defined both by age and disease conditions that more realistically reflect susceptible human populations. Subchronic and chronic exposures in these animals have not yet been carried out mainly because of the practicality of sustaining colonies of animals for long periods of time. There has also been an increased use of real-world particles, including CAPs and diesel, fine, and ultrafine particles.

This section discusses mechanistic areas in which particular progress has been made since 1997. In contrast to earlier approaches, whereby the mechanisms were explored by one specific experimental technique—for example, clinical studies, animal toxicology and in vitro studies—the field has progressed to the point that the data from these different disciplines can be integrated into a discussion of biological plausibility. The result has been the development of hypotheses that focus on specific areas, including (1) inflammation, both pulmonary and systemic, with perhaps a key role played by reactive oxygen species; (2) alteration in immune competence; and (3) autonomic nervous system dysfunction. Although these mechanisms will be discussed individually below, as shown in Figure C-2, they are undoubtedly interrelated.

Inflammation and Immunity

Airway injury and inflammation are well-known consequences of toxic inhalation exposures. Previous studies involving animal models have shown that instillation or inhalation of particles, such as diesel exhaust particles (DEPs), can cause inflammation and epithelial injury at high doses and concentrations. However, there was little evidence that exposure to ambient concentrations of PM cause significant airway inflammation. The presence or absence of an inflammatory response is an important issue, because inflammation can induce systemic effects, including an acute phase response with increased blood viscosity and coagulability, and possibly an increased risk for myocardial infarction inpatients with coronary artery disease. In chronic respiratory diseases, such as asthma and COPD, inflam-

mation is also a key pathophysiological feature. Chronic, repeated inflammatory changes of the airways may result in airway remodeling that result in irreversible lung disease. Thus, inflammation might be involved in both acute and chronic effects.

Recent controlled-exposure studies in humans indicate that several types of particles can induce an inflammatory response in the airways, the organ in which particles first deposit. Different experimental designs using CAPs, laboratory-generated carbonaceous ultrafine particles, and diesel particles have all provided evidence for effects on pulmonary or systemic markers of inflammation and leukocyte recruitment (Salvi et al. 1999; Ghio et al. 2000a,b; Frampton et al. 2001). For example, levels of cytokines, chemokines, and adhesion molecules following particle exposures in healthy humans have been altered in blood (Salvi et al. 1999; Frampton et al. 2001). These soluble molecules play an important role in blood cell recruitment to atherosclerotic lesions and inflamed airways. These findings suggest that exposure to either CAPs or ultrafine particles may initiate endothelial and leukocyte activation, a key initial step in leukocyte recruitment. Such observations may have important implications for cardiovascular and respiratory disease. In a major cardiac epidemiological study, such plasma markers were predictive of subsequent coronary events (Ridker et al. 1998).

Similarly, studies in normal dogs exposed to Boston CAPs by inhalation showed increases in pulmonary inflammation measured by bronchoalveolar lavage and in circulating blood neutrophils related to increases in specific ambient particle components (Clarke et al. 2000). Similar findings have been reported in rats exposed to CAPs and laboratory-generated particles (Saldiva et al. 2002). One possible consequence of damage to the airways is that the individual might become more susceptible to respiratory infections if exposed to viruses or bacteria. Inhalation exposure of bacterially infected rats to New York City CAPs for 5 hr resulted in alterations in both pulmonary and systemic immunity, as well as exacerbation of the infectious process. *Streptococcus pneumoniae* infected rats exposed to PM demonstrated increased burdens of pulmonary bacteria, numbers of circulating white blood cells, extent of pneumococcal-associated lung lesions, and incidence of bacteremia (Zelikoff et al. 1999). Subsequent studies implicated the iron content in mediating these effects. These findings suggest that PM exposure, especially the soluble iron or perhaps another metal component of PM, might affect the host immune response during pulmonary infection and might help to support epidemiological observations.

Cardiovascular Effects

Determining the mechanisms linking ambient PM to cardiovascular effects is one of the key challenges facing the research community. There is growing clinical and epidemiological evidence that ambient air pollution can precipitate acute cardiac events, such as angina pectoris, cardiac arrhythmias, and myocardial infarction, the majority of excess PM-related deaths being attributable to cardiovascular disease. Investigations of mechanisms of cardiovascular effects of PM have required multidisciplinary collaboration. Clinical studies of young and elderly subjects exposed to CAPs have shown reductions in heart rate variability (HRV) and increases in blood fibrinogen levels (Devlin et al. 2000, 2003). In another study, using frequency-domain analysis of the continuously recorded EKG, investigators found that responses of the parasympathetic nervous system were blunted during recovery from exercise immediately after exposure to ultrafine particles. In this study, exposure to ultrafine particles also altered cardiac repolarization (Frampton 2001; Frampton et al. 2002). Thus, a growing body of clinical evidence indicates that, even in healthy volunteers, there might be alterations in cardiac rhythm, implicating susceptibility to cardiac arrhythmias in patients with heart disease (Utell et al. 2002).

Similarly, animal studies are also linking exposure to PM with changes in cardiac function, including induction of arrhythmias and mechanisms explaining the increased incidence of myocardial infarction. Inhaled PM exacerbated ischemia in a clinically relevant model of coronary artery occlusion in conscious dogs. Exposure to CAPs significantly increased peak ST-segment elevation during a 5-min coronary artery occlusion (Wellenius et al. 2003). Exposure of aged rats to CAPs and spontaneously hypertensive rats to residual fly ash demonstrated increases in frequency of supraventricular arrhythmias and changes in ST segments, respectively (Kodavanti et al. 2000; Wellenius et al. 2003).

Investigators have focused on evaluating systemic inflammation and alterations in vascular endothelial function as a means to explain these cardiac phenomena. One marker of systemic inflammation detected after exposure to PM in humans, rats, and dogs is an increased number of circulating neutrophils (HEI 2002). Increased bone marrow production of immature neutrophils has also been reported (Suwa et al. 2002). Exposure to CAPs has been associated with higher levels of fibrinogen, resulting in an increased tendency to clot formation. That condition could prove to be particularly important in individuals with atherosclerotic plaque and narrowing of systemic and coronary vasculature.

Most recently, rats and humans exposed to ambient particles showed increased blood levels of endothelins, which affect vascular tone and endothelial function (Vincent et al. 2001a,b) Exposure of human volunteers to concentrated ambient particles in Toronto resulted in altered vascular tone assessed by an ultrasound technique (Brook et al. 2002).

In summary, an impressive array of findings from in vitro, animal and human studies provide a much more robust understanding of the potential mechanisms responsible for particle-induced cardiovascular events. Although a definitive mechanism has not been established to explain either the increase in cardiac arrhythmias or myocardial ischemia, it has become clear that particles are capable of producing many of the intermediate steps linked with adverse cardiac outcomes.

Oxidative Stress

Recent work focused on oxidative stress as an underlying mechanism that might be relevant to pulmonary, cardiovascular and other systemic effects. A major finding is that PM generates reactive oxygen species (ROS), which provide pro-inflammatory stimuli to bronchial epithelial cells and macrophages. These cellular targets respond with cytokine and chemokine production, which can enhance the response to allergens. Therefore, PM might act as an adjuvant that strengthens the response of the immune system to environmental allergens. Hallmarks of allergic inflammation include increased immunoglobulin E (IgE) production, eosinophilic bronchial inflammation, airway hyperresponsiveness, and an increase of NO in exhaled air. Animal studies and in vitro studies are testing this hypothesis using DEPs. DEPs markedly enhanced the antibody response and lipid peroxidation in allergic animals. Pretreatment with an antioxidant minimized the response (Whitekus et al. 2002). These findings are consistent with human nasal-challenge studies supporting the role of DEPs as an adjuvant in already established allergic responses, as well as in exposure to neoallergens. More recent studies have found that diesel exhaust inhalation increases inflammatory markers (such as lung neutrophils and eosinophils) in healthy volunteers, supporting the hypothesis that diesel exhaust can worsen respiratory symptoms. DEPs alone might augment levels of IgE, trigger eosinophil degranulation, stimulate release of various cytokines and chemokines, and stimulate the T_H2 pathway (Pandya et al. 2002). Taken together, these findings are possibly relevant in explaining the increased number and severity of asthma attacks in an urban setting related to in-

creased PM concentrations, and could implicate DEPs as a factor in asthma exacerbations. However, DEPs are not unique in that regard, because other particles, including carbon black, have been found to induce similar immunological effects (Maejima et al. 1997; Lovik et al. 1997).

ROS associated with exposure to PM might have a role in cardiovascular effects. Quinones and other compounds that produce ROS might contribute to disease-related vascular dysfunction caused by PM exposure. That possibility will become particularly relevant as the understanding of the role of PM in endothelial dysfunction expands and further explains the mechanisms responsible for the cardiovascular events.

Synthesis

Since 1997, reasonably consistent mechanistic findings from clinical and animal toxicology and in vitro studies have emerged to support the PM epidemiological findings. In particular, toxicological studies have supported the plausibility of PM systemic effects. The hypothetical mechanisms and mediators are diagrammed in Figures C-2 and C-3. Most recently, endothelial dysfunction has been suggested as a common mechanistic theme from epidemiological, clinical, and toxicological investigations.

Scientific Value

Understanding the mechanism of PM action is critical in providing biological plausibility for the epidemiological and toxicological findings. It provides a basis for understanding how PM can cause adverse health effects.

Decisionmaking Value

The convergence of the epidemiological and toxicological findings and an increased understanding of the mechanisms of PM toxicity has provided an important basis for the regulatory standard. In the absence of mechanistic data, there was skepticism about the interpretation of the epidemiological findings.

Information Expected in the Near Future

Given the diversity of health findings from the epidemiological studies, the committee anticipates continued refinement of the mechanistic basis for explaining adverse health effects resulting from PM exposure. Specific pathways of action are likely to be linked to specific physiochemical properties of PM. Although the toxicological findings have been at the physiological to cellular level, the future is likely to focus on molecular mechanisms and molecular epidemiology.

Remaining Major Uncertainties

- Relevance of mechanisms observed in animal and in vitro model systems to humans.
- Significance of high-dose exposure to low-concentration human environmental exposure.
- Absence of dose-response relationships.
- Relevance of no-physiological (such as instillation) routes of exposure to the normal inhalation route.
- Molecular mechanistic basis for the observed health effects.
- Relationship for the mechanism between acute and chronic health effects.

What Remains To Be Done?

Despite major progress since 1997, major uncertainties still exist in the scope and significance of experimental data in explaining the epidemiological findings on risks of PM. There are important limitations in the understanding of the relevance of mechanisms observed in animal and in in vitro systems for humans. Those limitations are particularly applicable to extrapolation from high-dose animal exposure to low-concentration human environmental exposures. Similar problems occur in understanding the relevance of mechanistic observations from nonphysiological exposure routes to the normal inhalation route of pollutant exposure. The findings from the clinical, animal, and in vitro experimental work have often not included dose-response relationships. The dose-response studies are an important element of confirming a mechanistic basis in support of the

epidemiological findings. In addition, similar physiological, cellular, and molecular responses to PM in different species help to provide a mechanistic underpinning to the epidemiological observations.

To date, the mechanistic observations have been largely in the area of physiological and cellular mechanisms. The molecular mechanistic basis for the observed health effects is yet to be explored but is a necessary approach in moving forward. Molecular mechanisms are likely to become increasingly important as the research community moves into the discipline of molecular epidemiology.

Finally, much of the exploratory, hypothesis-generating research done to date has focused on identifying mechanisms. The next step is to more clearly understand mechanisms underlying exposure-response relationships, recognizing that it is likely that most mechanisms will have some element of exposure (dose) dependence. This issue is critical to understanding the relevance of the various mechanisms described in experimental systems to ambient PM concentrations typically encountered by people.

RESEARCH TOPIC 10
ANALYSIS AND MEASUREMENT

To what extent does the choice of statistical methods in the analysis of data from epidemiological studies influence estimates of health risks from exposures to particulate matter? Can existing methods be improved? What is the effect of measurement error and misclassification on estimates of the association between air pollution and health?

Introduction

Statistical analysis is the basis for making inferences from data on air quality and health effects. Since the interpretation of the results may be tied to the analytical tools, it is necessary to develop and use appropriate methods for analysis and to understand the sensitivity of findings to the methods used. Several statistical models have been developed to analyze the temporal association between air quality measures and health. These models were widely used for analysis of time-series data related to both morbidity and mortality. The methods used to analyze these data have not been uniform across all studies; hence, it is important to understand the extent to which findings might be influenced by the methods used.

The committee's first report raised the issue of the critical timing of exposure (frequency or duration) in relation to the occurrence of the outcome. The many various studies have incorporated different intervals of time (lags) between pollution exposure and health outcomes, such as mortality. Use of different lags complicates comparisons of results across studies, particularly in regard to the time relationship between pollution exposure and resultant risk to health. To some extent, the differences in approach reflect the extent of existing air pollution measurement data; the availability of PM_{10} data on an every-sixth-day basis only for many locations has limited the extent to which lag structure can be addressed.

The committee's first report also addressed the issue of covariates in the models, including multiple pollutant measurements. The impact of pollution on life expectancy was another issue envisioned by the committee in its initial report.

State of Understanding in 1997

At the time of the committee's first report, several statistical models had been developed and applied to analyze the relationship between daily health outcomes and daily air quality measures. These models were widely used for analysis of time-series data related to both morbidity and mortality. The report noted, however, that many models introduced had not been "validated" and that it was "important to ensure that the conclusions reached are not dependent on the choice of method used." Other key issues, such as measurement error, harvesting,[2] and spatial analytical methods, had not yet been addressed rigorously but were recognized as methodological concerns in interpreting the findings of time-series studies. There was extensive statistical literature on measurement error; however, data on the magnitudes of measurement error for PM measures were not available. Harvesting had only been superficially addressed for a limited number of lag times. Literature on spatial autocorrelation was limited. Spatial autocorrelation had been largely ignored in studies that examined differences in air quality patterns and health effects across broad geographic areas.

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[2]The term "harvesting" refers to the question of whether deaths from air pollution occur in people who are highly susceptible and near death (and die a few days earlier because of air pollution than they otherwise would have) or whether the air pollution results in the deaths of people who are not otherwise near death.

The statistical literature provided a useful set of approaches that have now been applied to air pollution. The approaches include methods to aggregate results across studies or analyses and the use of factor analysis to develop a reduced set of pollution indices, which may be indicative of specific pollution sources.

What Has Been Learned?

In November 2002, EPA held a workshop to specifically address some methodological issues. The results and discussion from this workshop are also likely to contribute toward improving understanding of the use and influence of alternative methodological approaches.

Model Development and Application

Times-Series Models

Since 1997, several new methods have been introduced to analyze the temporal association between air quality and health effects; for example, daily counts of deaths in a given area have been related to daily PM concentrations in the days before the deaths occurred. A large number of such studies have been conducted. They provide significant evidence of the association between airborne PM and health effects. Previously, there had been no systematic comparison of the various methods used in the analyses. Some comparisons had suggested that many of the results were robust to the methods used. However, in a few cases, variation in input data (for example, pollution measures from different monitoring stations) has been shown to influence the results of the analysis (Lipfert et al. 2000b). In other cases, associations between health effects and air pollution have been robust to a variety of measures for weather.

Because of the variations in the models used to assess the association between air pollution and health, it has been difficult to compare results across locations. The NMMAPS study (Samet et al. 2000a,b) was a major effort designed partly to overcome that issue by applying the same methods to data from multiple locations. The NMMAPS approach used data from multiple cities selected solely on the basis of size across the United States, thereby avoiding bias from picking a particular city and assuring representativeness of the findings. The European Air Pollution and Health: A European Approach (APHEA) project also used common methods for several

cities (Katsouyanni et al. 2001). Reexamination of the NMMAPS data and analyses by the original investigators (Domenici et al. 2002) uncovered some problems in the software originally used in that study and in several others in this particular application. This examination found that the default software convergence criteria led to biases in associations estimated using LOESS procedures within the generalized additive model (GAM) framework. These biases were later shown not to be important in pooled estimates derived from the results from several cities (Samet et al. 2003). Further examination of these methods (Ramsey et al. 2003a) indicated that the standard errors of the measures of association were systematically underestimated, with the potential to lead to an increase in the apparent level of statistical significance.

Concern about these issues led EPA to convene a workshop on November 4-6, 2002, to discuss how published results were potentially affected by the previously used analytical methods. Investigators presented their results after applying several methods to the same data set. These results were published in 2003. For some data sets, the results appeared to be robust across several alternative methods that were applied. In other cases, the results differed, sometimes to the point that results would be statistically significant for one method but not another. These differences occurred not only within the widely used GAM framework but also between GAM and other approaches, such as the generalized linear model (GLM), and among assumptions used within the GLM modeling framework. For example, the GLM approach involves the use of several nonlinear parametric functions (splines) to estimate the seasonal pattern of daily mortality. Results can vary depending on the number of splines used to estimate the seasonal pattern. There is no consensus on the optimal number of splines that should be used, nor is it clear that the same number should be applied to each data set.

To date, there is no consensus about which method is "correct," as the implications of any effect on estimates from the choice of analytical method are not yet fully understood. Moreover, the implications of the analytical approach may differ from data set to data set. Researchers are confronted with an issue of estimating relatively small associations in the presence of confounding by weather and seasonality. Until the implications of alternative approaches are fully understood or until there is some scientific consensus about the "appropriate" method to use, researchers must explore the sensitivity of the results to alternative modeling approaches (Samet et al. 2000a).

Lags are also an important component of the specification of the analytical model for time-series studies. Treatment of lags has been nonuni-

form across studies, making complicating comparison of results. Some studies have examined only a small set of lags, with no consistency in the lags used across the studies. Other studies report results only for the lag that maximizes the association with the health variable. Other approaches involve distributed lags in which the magnitude of the association is assumed to be some function of the lag. The most helpful approach considers several lag combinations and reports results for all of them. As understanding of the biological mechanisms of PM improve, there may be greater consensus about the specific lag combination that should be used.

Some recent studies (for example, Peters et al. 2000) have examined shorter intervals (hours) between exposure and response and have found that the exposures with shorter lags are more highly associated with health response than lags up to one day. Unfortunately, continuous air quality data are not frequently available, as are data on the timing of health response. This issue will remain an important one to investigate and also raises an issue about the importance of peak exposures as opposed to average exposures in explaining health responses.

Times-series studies have also raised the issue of mortality displacement or harvesting; addressing whether those whose deaths are associated with pollution are either individuals whose deaths were imminent or individuals whose deaths were significantly advanced by pollution exposure. Several papers have advanced this topic through a variety of statistical approaches since 1997. Some recent studies (Zeger et al. 1999; Domenici et al. 2000; Schwartz 2000) report that the deaths associated with pollution from time-series studies do not reflect mortality displacement alone. Other approaches find that mortality displacement is particularly important (Smith et al. 1999; Murray and Nelson 2000). All of these papers have been tied to specific data sets. It would be useful to consider the alternative approaches to several of the same data sets.

Other Models

An alternative method of analysis of time-series data is provided by the case-crossover protocol (Checkoway et al. 2000; Lin et al. 2002). With this protocol, the exposure of an individual to ambient air pollution for a time period during which a health outcome (a case) occurred is compared with the exposure of the same individual for a different time period. Care must be taken in the choice of this comparison period (Lumley and Sheppard 2003). This method of analysis of time-series data does not require the complex smoothing and filtering of secular trends in the data and is not

subject to methodological problems associated with the generalized additive model. Because each subject effectively serves as his or her own control in the case-crossover analysis, this method affords some degree of control for the effects of unmeasured covariates. Lin et al. (2002) showed that the case-crossover design can be used to identify associations between short-term exposure to ambient air pollution and mortality, with risk estimates comparable to those obtained using time-series analysis. Fung et al. (2003) recently conducted a detailed comparison of the statistical properties of case-crossover and time-series methods.

In other areas, there have been some important improvements in modeling. For example, the issue of spatial autocorrelation was considered and addressed in one major study relating geographic gradients in mortality to those in pollution (Krewski et al. 2000). Burnett et al. (2001) proposed a simple method of taking into account spatial autocorrelation in such data. As in time-series analysis, however, consideration must be given to the effects of concurvity in spatial analyses (Ramsay et al. 20003a). Ma et al. (2003) developed a random-effects Cox regression model that allows for spatial patterns in the data through the use of random effects to describe clustering at the regional and metropolitan area level. Hughes et al. (2002) developed an efficient computer algorithm to implement this new survival analysis model. This work is currently being extended to encompass more than two levels of spatial clustering (Krewski 2004).

The Krewski et al. (2000) study serves as model in another sense. It examined a very large number of alternative analyses, undertaking an extensive sensitivity analysis. Given that results can vary according to analysis, other studies should be encouraged to undertaken similar sensitivity analyses. Unfortunately, most journals do not allow sufficient space to report the results of extensive sensitivity analyses. Approaches are needed on the part of both journals and investigators which permit full reporting of sensitivity analyses.

New approaches were developed by several authors (Beer and Ricci 1999; Murray and Nelson 2000; Sunyer et al. 2000; Tu and Piergorsch 2000; Zhang et al. 2000; Knudsen 2001). Given that some of the analytical results are sensitive to modeling approach, it will be important for developers of new approaches to indicate how their results compare with those that would be obtained using existing approaches.

Multipollutant Issues

The air quality data obtained from the EPA supersites, the EPA

speciation sites, and from special study sites will extensively increase the number of pollutant species that can be considered in analyses. These data can allow us to identify those pollution components that are of greatest health concern, but the availability of many pollution measures raises statistical issues. Because pollution concentrations are largely a function of meteorology and the amount of emissions from sources, many pollution measures are likely to be correlated. Correlations will be made especially in time-series studies where the amount of emissions is not likely to vary a great deal from day to day; hence, meterorological factors are likely to be particularly important in explaining pollutant concentrations. Hence, favorable meteorology is likely to allow higher concentrations of several pollutants on the same days. The resulting multicollinearity might make it very difficult to ascertain which of the pollutant measures is most highly associated with health response. As a minimum, it will require greater number of observations (data points) to allow discrimination among several pollution measures.

One method that has been used by several investigators (Ozkaynak et al. 1996b; Marr et al. 1999; Tsai et al. 2000; Laden et al. 2000) is to use factor analyses or pollutant indicators to identify classes of pollutants or sources of pollution that are more highly associated with the health responses. This approach resolves the multicollinearity problem, but it still does not identify the specific pollutants that may be of greatest health concern; it only identifies their source. These approaches need be scrutinized in more detail to ensure that the indices are consistent over seasons and geographic areas.

Aggregation Across Studies and Geographic Areas

There is statistical uncertainty present in any one result from any one study. For that reason, it is important to have several studies in an effort to confirm a result. One is then left with the task of synthesizing the results across studies. Several formal methods have been used to combine information across several studies and data sets in an effort to summarize and characterize the overall result. The statistical literature provides several methods that have been adapted for those types of analyses. New methods have been introduced to allow such pooling of results. The first general issue that must be addressed is whether pooling is warranted (Egger and Smith 1997). Clearly, if the studies have markedly different designs, it can hazardous to pool the results unless an accepted way has been found to adjust for differences across the studies. Another issue is whether the

results to be pooled can be assumed to come from the same statistical distribution. Data need to be tested for homogeneity to determine whether pooling is warranted. Then, a panoply of methods can be used to pool the data.

One of the most innovative approaches to pool results across studies is the use of Bayesian hierarchical models (Samet et al. 2000a,b), as were used to pool results from 90 cities in the NMMAPS study. Other approaches have been considered as well. Schwartz et al. used standard statistical approaches in combining results from six cities; Saez et al. (2001) applied an ecological-longitudinal model to carry out a pooled analysis of three Spanish cities; and Berhane and Thomas (2002) developed a two-stage model to combine results from several California locations.

Measurement Error

In epidemiological studies, the individual's exposure to pollutants of concern cannot be known for all relevant time averages. The difference between the actual exposure and the measured exposure is known as measurement error. Generally, three components are in this measure: errors due to instrument error; errors due to the unrepresentativeness of an air quality monitor; errors due to differences between the monitored pollution measures and the average actual exposure.

Zeger et al. (2000) developed a framework for measurement error in the context of air pollution epidemiological studies. They showed that under a wide range of circumstances, measurement error can result in underestimates of the association between air pollution variables and health. The major deficiency remaining in this area is high-quality data, which indicate the magnitude and statistical properties of measurement error. Several studies undertaken in recent years should be able to provide some of these data (see topics 1 and 2); however, these data have not yet been integrated into measurement error analyses.

Major Remaining Uncertainties

Times-Series Models

Researchers have begun to scrutinize the various modeling approaches and understand some of the weaknesses of the various approaches. It will be necessary to address these weaknesses. Second, researchers have seen

that in some cases the modeling approach can influence the result. It is paramount that these differences be understood and that investigators be encouraged to undertake sensitivity analyses so that it can be known which results are robust across methods and which are not.

There is still no major consensus on the treatment of lags. This issue is likely to become more complicated with the advent of more continuous air quality data. Methods need to be found to help define the most appropriate averaging times and lags for pollution variables in future analyses. Biological considerations could play an important part here.

The harvesting issue needs to be addressed more systematically in several data sets. A dialogue among investigators who use alternative approaches would be constructive for understanding where there is consensus and where there are differences. Some consideration might also be given to alternative study designs.

Other Models

As more biological data become available, the data will need to be incorporated into models. As new models and approaches are developed, it will be necessary to compare them to existing approaches and to understand whether the new ones have any influence on the outcomes of their analyses.

Multipollutant Issues

These issues will proliferate as more data become available. Resources need to be applied to define new and promising ways to address this issue.

Aggregation Across Studies and Geographic Areas

As the number of studies multiplies, objective methods to allow pooled estimates of effects or associations would be useful. Tools are available for that purpose; however, they might need to be adapted to the specific data characteristics of the studies for which data are available. In addition, it will be important to demonstrate that polled estimates are robust across a variety of approaches.

Measurement Error

The data that have been collected under topics 1 and 2 will need to be analyzed to understand the statistical properties and distributions of measurement error for the various pollutants. These need to be incorporated into the frameworks that have been developed. With the use of multiple regression models (with several pollutants) and nonlinear models, new frameworks will need to be developed (Carroll et al. 1995).

What Remains To Be Done?

The framework that has been developed and its limited application suggest that measurement error per se will not negate the positive associations found between air pollution and health. More precise estimates of the magnitudes and statistical distributions of measurement error need be incorporated into multipollutant models to provide more reliable quantitative estimates of the impact of measurement error and of the relative importance of the various pollutants on health impacts. Greater consideration of this issue will give more credence to risk assessments used to support regulatory decisions.

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