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Particulate Matter Research Program

Five Years of Progress

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Abstract

This report summarizes the major accomplishments of the U.S. Environmental Protection Agency's Particulate Matter (PM) Research Program achieved since 1997. Among the most notable achievements is that scientists have quantitatively established that exposure to ambient particulate matter (PM) is associated with morbidity and mortality. Significant progress has also been made in understanding the influence of PM size and composition on unwanted health outcomes, in uncovering the biological mechanisms which link PM exposure to adverse health outcomes, and in discovering the human characteristics which increase susceptibility to adverse health outcomes. Additionally, advances in PM science have provided information about the deposition and fate of particulates in the respiratory tract as well as about the sources of particulate air pollution and about the atmospheric processes that influence PM chemistry and transport. These research outcomes provide the basis for scientifically defensible regulatory actions and support the Agency's ongoing mission of ensuring that the air in every American community is safe and healthy to breathe.

Foreword

With this report, I am proud to present a summary of the major accomplishments achieved by the U.S. Environmental Protection Agency's Particulate Matter (PM) Research Program since the promulgation of the National Ambient Air Quality Standards for PM in 1997. Among the most notable achievements is that Agency scientists and our research partners have quantitatively established that exposure to ambient PM is associated with morbidity and mortality. We have also made significant progress in understanding the influence of PM size and composition on unwanted health outcomes, in uncovering the biological mechanisms which link PM exposure to adverse health outcomes, and in discovering the human characteristics which increase susceptibility to adverse health outcomes. Additionally, we have learned important information about the deposition and fate of particulates in the respiratory tract as well as about the sources of particulate air pollution and about the atmospheric processes that influence PM chemistry and transport.

These accomplishments are the product of a successful and ongoing collaborative research performed by Agency scientists, extramural investigators funded by EPA, and partners such as the Health Effects Institute (HEI). Other Federal organizations (including the National Institutes of Health and the Department of Energy) and others participating in the Air Quality Research Subcommittee of the Federal Committee on Environment and Natural Resources (CENR) have also made substantial contributions to our efforts to advance PM science.

The advancements in PM science achieved through these partnerships since 1997 provide a sound basis for scientifically defensible regulatory actions. Bolstered by these successes and driven by a sustained commitment to ensuring that the air in every American community is safe and healthy to breathe, the Agency will continuing our efforts to better understand the complex issues associated with particulate matter.

Paul Gilman, Ph.D.
Assistant Administrator

Contents

Acronyms and Abbreviations

ACS	American Cancer Society
ANS	autonomic nervous system
AQCD	Air Quality Criteria Document
CAA	Clean Air Act
CAFO	concentrated animal feeding operations
CAP	concentrated ambient particle
CASAC	Clean Air Scientific Advisory Committee
CENR	Committee on Environment and Natural Resources
CFR	Code of Federal Regulations
CMAQ	Community Multiscale Air Quality
CMB	chemical mass balance
COH	coefficient of haze
COPD	chronic obstructive pulmonary disease
CVD	cardiovascular disease
DEP	diesel exhaust particle
DMA-APM	differential mobility analyzer-aerosol particle mass analyzer
EC	elemental carbon
ECG	electrocardiogram
EMEFS	Eulerian Model Evaluation Field Study
EPA	U.S. Environmental Protection Agency
EPRI	Electric Power Research Institute
ESFF	electrostatically-enhanced fabric filter
ESP	Eastern Supersites Program or electrostatic precipitator
FGD	flue gas desulfurization
FRMs	Federal reference methods
FTIR	Fourier transform infared
GAMs	general additive models
HEI	Health Effects Institute
HF	high frequency
HR	heart rate
HRV	heart rate variability
MI	myocardial infarction
MYP	Multi-year Plan
NAAQS	National Ambient Air Quality Standard
NanoMOUDI	Nano Micro-Orifice Uniform Deposit Impactor
NARSTO	North American Research Strategy for Ozone
NCEA	National Center for Environmental Assessment (EPA)
NCER	National Center for Environmental Research (EPA)
NE-OPS	Northeast - Oxidant and Particle Study
NERL	National Exposure Research Laboratory (EPA)
NHEERL	National Health and Environmental Effects Research Laboratory (EPA)
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIST	National Institute of Standards and Technology

NMMAPS	National Morbidity, Mortality, and Air Pollution Study
NRC	National Research Council
NRMRL	National Risk Management Research Laboratory (EPA)
NYU	New York University
OAQPS	Office of Air Quality, Planning, and Standards (EPA)
OAR	Office of Air and Radiation (EPA)
OC	organic carbon
ORD	Office of Research and Development (EPA)
PAHs	polycyclic aromatic hydrocarbons
PCM	particle composition monitor
PM	particulate matter
PMF	positive matrix factorization
PM_x	particulate matter smaller than x symbolmuμm in aerodynamic diameter
RFA	Requests for Applications
ROFA	residual oil fly ash
SAB	Science Advisory Board (EPA)
SAMI	Southern Appalachian Mountains Initiative
SCISSAP	Southern Center for the Integrated Study of Secondary Air Pollutants
SCR	selective catalytic reduction
SDNN	standard deviation of normal to normal
SEM	scanning electron microscope
SHEDS	Stochastic Human Exposure and Dose Simulation
sICAM-1	soluble intercellular adhesion molecule-1
SIP	State Implementation Plan
SMVGEAR	Spars-Matrix, Vectorized Gear Code
SOA	secondary organic aerosol
SOS	Southern Oxidant Study
STAR	Science To Achieve Results
STN	Speciation Trends Network
SVOC	semivolatile organic compound
TEOM	tapered element oscillating microbalance
TOFMS	time-of-flight mass spectrometry
TSP	total suspended particulate
TVA	Tennessee Valley Authority
UCLA	University of California, Los Angeles
VOC	volatile organic compound
XRF	X-ray fluorescence

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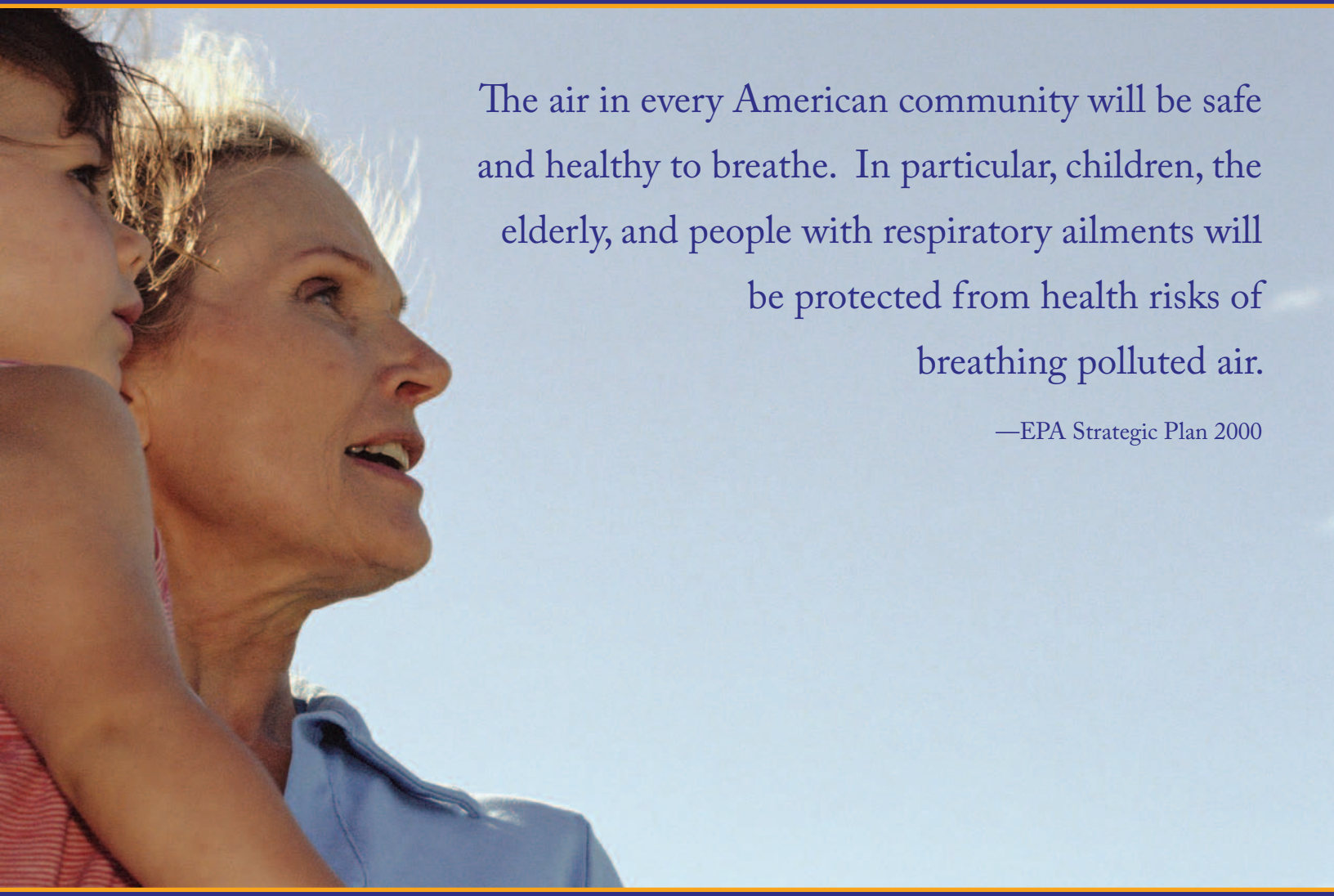

The air in every American community will be safe and healthy to breathe. In particular, children, the elderly, and people with respiratory ailments will be protected from health risks of breathing polluted air.

—EPA Strategic Plan 2000

Introduction

Purpose and Content of this Report

By 1996, evidence had accumulated that suggested day-to-day exposures to ambient particulate matter (PM) at or near the level of the then current National Ambient Air Quality Standards (NAAQS) were eliciting significant human health effects in the U.S. population, including hospitalizations and attributable deaths. This evidence led to the promulgation of PM NAAQS in 1997 that included new standards for PM smaller than 2.5 μm in aerodynamic diameter ($PM_{2.5}$).[1] Uncertainties regarding PM health effects prompted Congress to augment the President's recommended U.S. Environmental Protection Agency (EPA) budget of $27.8 million for PM research in 1998 by $22.4 million, and this level of investment in PM research has been largely maintained since that time. EPA was charged with accelerating investigations of the role of PM in air pollution-associated health outcomes and implementing health risk reductions via scientifically defensible regulatory actions.

Five years of intensive research activity have yielded significant advances in the understanding of the role of PM in causing health effects. In general, the advances lie in three broad areas: (a) the complex roles of PM attributes and human host factors that contribute to the health outcomes and (b) the factors determining public and individual exposures, and (c) the characterization of the sources and atmospheric processes. A comprehensive national research endeavor was initiated by EPA in 1998 and currently involves the coordinated efforts of intramural and EPA-funded extramural investigators, partners, and other federal organizations that function within a scientific framework of research needs developed by an independent National Academy of Sciences National Research Council (NRC) committee of experts.

Yet, while much has been learned in this timeframe – the first steps of an ambitious long-range plan – there remains considerable uncertainty regarding PM-associated health effects. For example, the research concerning the components and attributes of PM has raised several hypotheses that may help explain relationships between particles and health and thus require further investigation, perhaps within the context of source profiling and attribution. With the discovery that many of the adverse responses to PM exposure appear in individuals who are members of susceptible subpopulations, futher research is needed on the factors and mechanisms that underlie susceptibility. And finally, there are uncertainties regarding potential long-term health outcomes – from exposure measurements to quantifying the extent of possible life-shortening.

[1]The standard nomenclature is to refer to PM smaller than *x* μm in aerodynamic diameter as PM_x. The use of PM_{x-y} indicates particles between *x* and *y* μm in aerodynamic diameter.

The goal of these efforts, of course, is to provide health data appropriate to the review of the NAAQS. In addition, regulators at the federal and state levels who must implement the NAAQS depend on predictive and evaluative tools to determine compliance and to develop the needed mitigation strategies. As the understanding of atmospheric processes and source-to-receptor relationships improves, these tools are refined with new data and thus are ever-evolving. Research to refine the databases, reference methods, and atmospheric models that support regulatory needs is crucial to the mission of the EPA Office of Research and Development (ORD) PM Research Program.

This report is intended to summarize and highlight the salient EPA-funded scientific advances in PM health, exposure, and implementation research since 1997. The following discussion is framed according to the priority research needs noted in the four NRC reports published to date (specifically the third report,[2] which is outlined in a following section) and in the context of the programmatic and regulatory needs of EPA's Office of Air and Radiation (OAR). To simplify the "Major Accomplishments" narrative for each research topic, EPA and/or ORD are used to designate the PM Research Program and only selected prominent or illustrative publications are referenced in the text. (Appendix A is a complete reference list of publications from EPA-funded research. Appendix B lists studies funded by EPA partners or other organizations; these studies are also referenced in the report for continuity or completeness.) Finally, using the state-of-the-art techniques as reported herein, the envisioned future directions and goals for the specific research topic area research efforts are also discussed.

Setting the Stage

Episodes of choking air pollution, such as those experienced in Donora, PA, in 1948 and New York City, NY, in 1962, are extremely rare events in the modern-day U.S. Almost four decades of regulatory actions and technological advances in emission control have substantially reduced the overt threat of severe air pollution. However, contaminated air in the U.S. continues to have widespread effects on human health and the environment. For example, EPA estimates that current regulations to reduce air pollution can prevent tens of thousands of premature deaths per year and prevent perhaps hundreds of thousands of annual hospitalizations for cardiovascular and respiratory illness (1). The monetary benefits of preventing air-pollution-related premature deaths are estimated to be in the range of $100 billion per year. The benefits of reducing illness and minimizing the number of lost workdays and the consequences of restricted activity are estimated to provide an additional savings on the order of $10 billion per year. However, these cost estimates likely underestimate the true human toll when the costs

[2]The fourth and final NRC report on PM research priorities was released as this report was in preparation. Because the third and fourth reports were structured around the same 10 priority research areas, as is this report, and because this report discusses the accomplishments of the research program prior to the fourth report's completion, this document was not modified in response to the final NRC report.

associated with the loss of quality of life are considered. Underscoring the issue is the fact that these effects appear to affect certain subgroups more than others, including the elderly, the young, and those with pre-existing cardiopulmonary problems. To address these concerns, EPA developed a Clean Air Goal:

The air in every American community will be safe and healthy to breathe. In particular, children, the elderly, and people with respiratory ailments will be protected from health risks of breathing polluted air.

By the mid-1970s, the air looked cleaner; likewise, conventional epidemiology indicated that the associated health problems were largely eliminated. However, beginning in the late 1980s and throughout the 1990s, the novel application of sensitive statistical methods to epidemiological assessments of daily patterns of air pollution revealed that significant health risks remained, most notably those associated with ambient PM. Effects on mortality and morbidity were found at lower concentrations than formerly appreciated. Most striking was that these effects were observed at levels at or below the NAAQS for PM_{10} contemporary with the studies. Perhaps less surprisingly, those most affected represented groups who generally might be considered susceptible—the elderly and those with pre-existing cardiopulmonary disabilities. Moreover, a more limited study suggested that chronic PM exposure could potentially shorten life-spans in the general population (2).

Under the Clean Air Act (CAA), PM is one of six major air pollutants for which EPA has established a NAAQS. The CAA requires periodic review of the scientific basis or "criteria" for these standards and calls for EPA to lead the preparation of a comprehensive scientific assessment of the state of the knowledge for each criteria air pollutant.[3] The 1996 "Air Quality Criteria for Particulate Matter Document" (PM AQCD) (2) provided the scientific basis for the current PM NAAQS set in 1997. At present, 5 years hence, a revised and updated draft PM AQCD has undergone several reviews by the Clean Air Scientific Advisory Committee (CASAC) and the public.[4] The Fourth External Review Draft of the PM AQCD (4) was reviewed by CASAC in August 2003; the final revision will be released in 2004.

[3]The six criteria air pollutants are carbon monoxide (CO), lead (Pb), nitrogen dioxide (NO_2), ozone (O_3), PM, and sulfur dioxide (SO_2).

[4]Due to recent revelations of problems associated with the use of certain widely-used statistical software packages in a number of published statistical analyses of PM epidemiological data, the fourth draft of the document includes a discussion of re-analyses of a subset of PM epidemiological studies considered to be of particular relevance to the PM NAAQS review. Before the revisions to the fourth draft of the PM AQCD were completed, an expert panel assembled by the Health Effects Institute (HEI) published a peer-reviewed compilation of short communications summarizing appropriate re-analyses for affected studies addressed in an EPA workshop held November 4–6, 2002. HEI then completed a report (3) containing the re-analyses, short communications, and commentary by its peer review panel.

The latest PM AQCD includes discussion of the extensive body of newly available PM research information that has been published since the publication of the 1996 PM AQCD. This includes numerous published studies generated by EPA's PM Research Program (both intramural and extramural components), which, starting in 1998, was rapidly expanded in order to further advance the scientific bases underlying future PM NAAQS decisions. The expanded EPA PM Research Program was initiated as an integrated cross-lab and cross-center effort with high levels of interaction with OAR and cooperation with other federal agencies, partners, and academia. With the development of a Multi-Year Plan (MYP) describing the long-term research priorities, the EPA PM Research Program is forward-looking and evolving with advances in the science and with the needs of the regulatory community. Priorities set forth in the MYP are guided by the research needs and priorities set forth by the NRC Committee on Research Priorities for Airborne Particulate Matter and the science needs of OAR to set and implement the PM NAAQS.

Research Planning and Related Activities

In 1997, the President emphasized urgent concern about PM when the new NAAQS was announced: "The EPA, in partnership with other federal agencies, will develop a greatly expanded coordinated interagency PM research program. The program will contribute to expanding the science associated with particulate matter health effects, as well as developing improved monitoring methods and cost-effective mitigation strategies (5)." This directive, coupled with additional funds appropriated by Congress, charged EPA to refine the assessment of PM health risks and to explore methods to minimize these risks though monitoring and improved control measures.

The NRC Committee

To implement this expanded program, Congress asked EPA to arrange for an independent study by the National Academy of Sciences through a specially convened NRC panel, the NRC Committee on Research Priorities for Airborne Particulate Matter (hereafter referred to as the NRC Committee). The purposes of the NRC Committee study were as follows: (a) to develop priorities for a comprehensive PM research plan; (b) to develop an outline for a PM research program that addressed near- and long-term questions; and (c) to develop a plan to monitor research progress over the ensuing 5 years. EPA's PM research planning process began immediately following the release of the 1996 PM AQCD. A public workshop was held which produced a peer-reviewed document entitled "Particulate Matter Research Needs for Human Health Risk Assessment To Support Future Reviews of the National Standards for Particulate Matter" (6).

Drawing from this document, a preliminary workplan developed by EPA staff, and the panel's broad range of expertise on the topic, the NRC Committee prepared its initial report in 1998. It has published a total of four reports: "Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio" (7); "II: Evaluating Research Progress and Updating the Portfolio" (8); and "III: Early Research Progress" (9); and "IV: Continuing Research Progress" (10). The fourth and final report provides an assessment of research progress over the five years of the PM Research Program and outlines a vision of research priorities and needs meriting attention in coming years. In the published reports, the NRC Committee identified important research topic areas and recommended a multi-year portfolio and approach to address the highest priority research topics designed to strengthen and expand the scientific understanding of the links between ambient PM and adverse health effects. In its initial report, the NRC Committee did not consider research activities associated with implementing the NAAQS (11). It has since expanded its review of EPA's PM Research Program to include implementation-related research in recognition of the close connections between implementation and health effects.

EPA Research Planning Activities

In 1998, EPA developed an internal draft research strategy that encompassed the NRC Committee's recommended research priorities. This research strategy also drew from documents and presentations of a cross-section of groups in both the public and private sector, including other federal organizations and agencies (e.g., the Committee on Environment and Natural Resources, or CENR, discussed later in this report); various state agencies; research partners (e.g., HEI); private groups (e.g., the Electric Power Research Institute, or EPRI); and other scientific institutions (e.g., National Institutes of Health, or NIH); and universities. The result was the development of a focused, comprehensive, and coordinated program of PM research spanning the risk identification/assessment/management paradigm.

This draft strategy was translated into a working document, the MYP, which could be used for internal program planning and the evaluation of progress. The MYP outlines the direction of the program with long-term and annual goals; has associated specific measures of performance, achievement, and productivity along well-defined pathways; and includes timelines for each long-term goal. Even though the MYP establishes a strategy, it is used as a living document that is reviewed quarterly to assess progress and is revised biannually in the context of OAR regulatory and science program needs. To oversee coordinated PM research efforts across ORD, across the Agency, and among EPA's partners in the public and private sectors, ORD established the position of National Program Director for PM. This person facilitates cooperation and communication about these research activities, both internally and externally, and is responsible for ensuring that the research program is meeting EPA's science needs related to PM. EPA's other offices, including the EPA Regional Offices, have also made substantive contributions to the development of the MYP, its review, and resource alignments. The MYP also identifies areas of research that can benefit other EPA research programs to maximize the impact from each research investment.

Grants Focused on PM Research

One component of EPA's research strategy is the extramural grants program. The Science to Achieve Results (STAR) Program, managed by the National Center for Environmental Research (NCER), funds research grants in numerous environmental science, engineering, and health disciplines through a competitive solicitation process and independent peer review. The program engages the nation's best scientists and engineers in targeted research that complements EPA's own intramural research program and those of its partners and other federal agencies. The focus of the STAR research program for air has been structured around the priorities identified in the NRC Committee reports, as well as EPA's PM strategy and MYP. Requests for Applications (RFAs) are developed by a team of experts from the ORD labs and OAR to ensure that the research funded will address high programmatic priorities and be an integral part of the total research program. In eight years since 1995, the STAR program has awarded 77 research grants related directly to PM research. The research generated by way of the STAR Program has significantly expanded the scientific literature on PM health effects, exposure, emission sources, and atmospheric transformations.

PM Research Centers

In the 1998 EPA Appropriations Bill, Congress directed EPA to establish as many as five PM university research centers as part of the expanded ORD PM Research Program. The PM Research Centers Program began in 1999 with a STAR Program RFA. The RFA was structured around the research areas identified in the NRC Committee's 1998 report "Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio" (7). Of the 20 applications received, five university PM research centers were selected, and their work is adding greatly to the body of knowledge related to PM health effects and exposure. While all of the PM research centers are investigating the health effects of PM, each has a different focus. Harvard University is focusing on urban PM exposure, susceptible populations, and biological mechanisms. New York University (NYU) work targets specific PM components and size fractions. The University of Washington's Northwest PM Research Center focuses on the contributions of wood smoke, agricultural burning, and wildfires to ambient PM. A consortium of southern California universities, led by the University of California, Los Angeles (UCLA), is focusing on PM pollution from mobile sources. The University of Rochester's PM Research Center is working to understand the behavior and health effects of ultrafine particles.

In a somewhat unprecedented manner, the ORD in-house PM Research Program is often considered the sixth PM Research Center of the EPA PM Research Program as a means to prevent redundant efforts and ensure a coherent approach across the entire program. Over time, the National Program Director for PM has worked with the extramural PM research center directors to develop productive liaisons with and between the five PM research centers, emphasizing research communication and, to the extent possible, collaboration. The PM research center directors and selected staff meet annually among themselves and with EPA science managers and staff to discuss research progress, future directions, and organizational issues. The extramural PM research centers have prepared an interim report for the first two and a half years of funded work which was reviewed by a subcommittee of EPA's Science Advisory Board (SAB) to assess the advantages and shortcomings of the PM-research-centers concept and the value of cross-center integration (12,13). The report found favorably for the benefits of the centers to the EPA PM Research Program and for the scientific value of their integrated efforts. Additionally, the report made several suggestions for improving interactions among the centers and with the EPA in-house PM Research Program.

PM Supersites Program

The PM Supersites Program was established as an ambient monitoring research program intended to address the scientific uncertainties associated with characterization and measurement of fine PM in the atmosphere. The program was funded primarily by OAR and has benefited from extensive ORD participation. In the early stages of the program, OAR worked with ORD to develop a PM "Supersites Conceptual Plan" (http://www.epa.gov/ttn/amtic/files/ambient/pm25/casac/ssconpl2.pdf) and held a public PM Measurements Research Workshop in Chapel Hill, NC, on June 22–23, 1998. The workshop was attended by about 200 members of the atmospheric, exposure, and health effects research communities. Seven Supersites[5] were funded in the second phase of the program to study advanced ambient monitoring and measurement methods and atmospheric chemistry. The interactions between OAR, ORD, and the Supersites Program participants have provided strong technical guidance to ORD's internal research on ambient monitoring and atmospheric chemistry and have also enabled the Supersites Program to maintain focus on the questions of most importance to OAR and ORD.

[5]The Supersites are located in Los Angeles and Fresno, CA; Houston, TX; St. Louis, MO; Pittsburgh, PA; Baltimore, MD; and New York, NY.

Health Effects Institute

HEI has been a key partner in PM research. It is an independent, nonprofit corporation chartered in 1980 to provide high quality, impartial, and relevant science on the health effects of environmental pollutants. Supported jointly by EPA and industry, HEI has funded over 170 studies and has published more than 100 research reports and several special reports. Particulate air pollution is identified as a priority in the HEI Strategic Plan (14), and this public/private partnership has made significant advances in PM-related research. HEI has worked closely with the epidemiology community to solidify its database and analyses of large urban studies (e.g., the National Morbidity, Mortality, and Air Pollution Study, or NMMAPS), as well as to provide opportunities for investigations of health (mechanisms), statistics (general additive models, or GAMs, used in epidemiology), and effects of changing technology (e.g., diesel engines). An internal EPA coordination committee facilitates communication between EPA and HEI concerning research priorities and direction. The research supported by HEI is highly relevant to the mission of EPA's air quality programs and complements EPA's in-house PM Research Program well, especially in the area of epidemiology.

ORD In-House Research

With the MYP as its guide, the in-house research conducted by ORD and the extramural program administered by NCER integrate the diverse capabilities of staff and extramural grantees in health, exposure, atmospheric, and engineering sciences of the National Health and Environmental Effects Research Laboratory (NHEERL), the National Risk Management Research Laboratory (NRMRL), the National Center for Environmental Assessment (NCEA), and the National Exposure Research Laboratory (NERL). The in-house research program balances the long- and short-term needs of the regulatory program and aims to investigate the health and exposure issues, atmospheric process, and source-to-receptor relationships that must be understood in order to set standards to protect human health and to develop models, tools, and data for the states and EPA regions to use in their development of State Implementation Plans (SIPs) to meet and enforce the NAAQS. ORD scientists work closely with OAR to develop monitoring methods (e.g., Federal Reference Methods, or FRMs, and methods for PM components and precursors) and strategies to acquire not only the mandated data for implementation and enforcement, but also to provide opportunities for adjunct health research to address risk and accountability questions.

Integration with Other Federal Agencies, the Private Sector, and Other Governmental Organizations

The President's call for a greatly expanded and coordinated interagency PM research effort led to the creation, in 1999, of the Particulate Matter Workgroup, which is administered by the Air Quality Research Subcommittee of CENR (15). This workgroup, co-chaired by EPA and the National Institute of Environmental and Health Sciences (NIEHS), meets bi-monthly with a goal of "enhancing the scientific information base for public policy that protects the public health (of primary importance) and the environment from harmful effects due to airborne particulate matter." This goal is to be accomplished by meeting three objectives: (a) "integrate health, exposure, ecology, atmospheric process, and source characterization research pertaining to particulate matter;" (b) "coordinate efforts among U.S. federal agencies and, as feasible, the private sector;" and (c) "address the highest priority research needs first, to inform public policy choices for standard setting and air quality management." The workgroup is comprised of 22 member agencies (listed in Appendix C). The workgroup has completed and recently released its "Strategic Research Plan for Particulate Matter" (16). This plan will guide the coordinated federal research program over the next 5 to 10 years. The document outlines the workgroup's current understanding of the PM issue, identifies selected recent accomplishments in each of its major discipline areas, and identifies key information gaps within priority research needs.

Integrating the body of national PM research dealing with atmospheric sciences is accomplished under NARSTO, the multi-stakeholder entity organized in 1994 to sponsor cooperative public/private policy-relevant research on tropospheric ozone.[6] NARSTO's mission was expanded in 1998 to include ambient PM. Its membership of more than 65 organizations includes all major federal, state, and provincial governments; private industry; and utility sponsors of atmospheric sciences research in Canada, Mexico, and the U.S. EPA is a charter member of NARSTO. Its focus is PM-source-receptor relationships as understood through the study of emissions characterization, atmospheric measurement, processes, and modeling. NARSTO research is guided by its "Strategic Execution Plan," specifically "Part IV: PM Science Plan," (17). NARSTO recently released an assessment of PM atmospheric science, "Particulate Matter Science for Policy Makers: A NARSTO Assessment" (18). The primary purpose of this assessment is to assist policy makers in all three countries as they implement their national air quality standards for PM. It presents the latest understanding of the PM atmospheric phenomena over North America, and, when gaps in knowledge are identified, recommends additional work to fill them.

[6]Formerly an acronym for the North American Strategy for Tropospheric Ozone, the term NARSTO has become simply a wordmark signifying this tri-national, public-private partnership which deals with multiple features of tropospheric pollution, including ozone and suspended PM.

Five Years of Progress

Because much of the ORD research portfolio and MYP align with the NRC Committee's priority research topics, this report is also organized in that context. Each section in this report corresponds to one of the NRC priority research topics, and the key scientific question posed by the NRC for that topic is highlighted on the topic's title page. A significant portion of ORD's implementation research agenda was subsumed by what was referred to as Technical Support in the third NRC Committee report. To better describe this part of the agenda, this topic is discussed in the "`Research Topic 11." Technical Support—Atmospheric Measurements and Methods" section of this report.

The ORD health research program that supports the development of the NAAQS continues to pursue the unresolved issues of causality relative to PM characteristics and constituents, but has gradually shifted perspective to focus on how PM attributes are linked to their sources. Because many constituents of PM appear to have toxicity implications (perhaps as mixtures), source-attributed PM rather than individual components may better relate to risk and may better target control strategies. Meanwhile, topics of growing interest include understanding the role of susceptibility in PM responses and identifying attributes that may be common across susceptible groups. Another area of concern is the potential for long-term adverse health outcomes or life shortening as has been suggested by the recent reassessment of the American Cancer Society (ACS) database. Each of these issues will be explored by ORD in the next several years.

With over three years of $PM_{2.5}$ monitoring data now available from the National Monitoring Network, there is a pressing need for accelerated implementation-related research (emission measurement and characterization, regional and local atmospheric modeling for PM, and ambient measurement methods). In 2004, EPA is making attainment designations on the basis of monitoring and modeling data; the tribes, states and EPA regions must then develop and review requisite SIPs to meet the current NAAQS. Similarly, the availability of the Supersites Program database for study, methods development, and validation for important PM constituents (such as organic and elemental carbon, or OC and EC) will provide valuable information for final SIP implementation. Thus, the ORD PM Research Program, with its diverse yet targeted research agenda, is working to balance cyclic and tactical needs in order to meet mandated milestones within the context of its strategic MYP.

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A participant in a PM personal exposure study.

Outdoor Measures Versus Actual Human Exposures

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

Introduction

The epidemiological studies that provided much of the scientific basis for the PM NAAQS of 1997 indicated that increased risks of mortality and morbidity are associated with ambient PM across a wide range of concentrations. A remarkable feature of these studies is the strength of the concentration-response relationship between data from community monitors and a human population that spends most of its time indoors. It is almost counterintuitive that monitors representing the widely distributed PM mass within a given airshed could serve as a surrogate for individual human exposures given the diversity of lifestyles and activities. Indeed, those found to be most at risk, including the elderly and individuals with coronary or respiratory disease, are least likely to be exposed to PM in the outdoor environment, that is measured by ambient monitors. Additionally, data from early studies suggested that personal PM exposures may differ substantially from outdoor concentrations due to contributions from indoor sources. Cross-sectional analyses of previous data also showed weak associations between daily outdoor PM concentrations and corresponding personal exposures. This disparity was attributed to inter-subject variability and the limited number of measurements (1–2 days) for any given individual. In 1997, databases that were fully adequate for relating ambient PM mass measurements to human exposures did not exist. The relationship between outdoor PM and the amount that penetrated indoors was only partially understood, as was the significance of the range of ambient, indoor, and personal sources that contributed to total personal exposure.

ORD recognized the fundamental need to link outdoor PM to personal exposure early on. Understanding the source-to-personal exposure component of the risk paradigm became a primary concern of ORD's PM Research Program. Specifically, understanding the relationship between PM measured at community monitors and local outdoor, indoor, and personal exposure concentrations was considered essential to understanding health risks. Likewise, the effect that human activities and other factors had on these relationships required investigation; consequently ORD initiated research in this area in 1997. Field studies, laboratory studies, and model-development research have been combined to quantify important relationships and to understand how subpopulations, regions, seasons, housing type, and human activities affect these relationships.

Key Uncertainties, Objectives, and Special Issues

When the revised NAAQS was promulgated in 1997, these questions about the relationship between PM measured at ambient sites and personal exposure remained a key area of uncertainty. Thus, understanding personal exposures to PM provides the critical link between regulatory monitoring of ambient air and personal health outcomes that is fundamental to the scientific underpinnings of the new NAAQS. The overall goal of EPA's exposure program has been to develop data and models that characterize and predict human exposure to PM relative to that measured at ambient sites. Three research objectives were established with a particular focus on susceptible subpopulations:

- To characterize exposure scenarios and to collect data with which to evaluate and quantify the relationship between the attributes of exposure (magnitude, frequency, and duration) and ambient PM and co-pollutants as measured at community sites for the general and susceptible populations;
- To develope exposure models that characterize and predict the exposure (magnitude, frequency, and duration) of the general and susceptible populations to PM and co-pollutants relative to that measured at ambient sites; and
- To use these exposure models to link atmospheric dispersion and lung deposition models in order to generate estimates of the source-air-exposure-dose relationships for input into a risk-assessment analysis.

Research was conducted in several areas to address these objectives comprehensively. Longitudinal PM exposure studies were conducted to characterize inter-personal and intra-personal variability in exposure to PM mass and to describe the relationship between personal exposures and ambient exposure estimates based on central-site monitoring. Detailed laboratory and field studies were conducted to characterize the physical and chemical factors that determine the contribution of outdoor PM to indoor concentrations and personal exposures. The modeling research then was used to develop a conceptual framework and a first-generation human exposure model for PM mass that could describe both uncertainty and variability of exposure distributions within the population.

Data collection requirements for this research area were comprehensive, extending from the level of the community monitor to the individual. Personal exposure monitoring for PM and co-pollutants was, in some cases, conducted for as long as 28 days on elderly and cardiopulmonary-compromised participants. The specialized battery-powered instruments used were high sensitivity, low burden, lightweight and quiet. Because of the inherent variability, a large number of studies were required in order to fairly evaluate the effect of airshed, subpopulation, season, housing type, housing ventilation, and human activity on the exposure relationships. This research effort was the result of close collaborations between EPA intramural and extramural scientists. Data collected to date are under evaluation and are available for rigorous statistical analysis, as well as for use in the development or verification of exposure models.

Major Accomplishments

Research in this area has been ongoing since 1997; and much of the research, as projected by the NRC research portfolio timeline, has been completed. Data analysis is continuing in an effort to understand the important factors that influence various cohort exposures in different areas of the country during different seasons. Through collaborative research partnerships, ORD has successfully developed the tools and models to reasonably quantify and predict the relationship between ambient site measurements and personal exposure for PM mass. The findings from recent longitudinal PM exposure studies have been critical to the evolution of exposure assessments for PM mass, which can now be made using high quality data and models.

Longitudinal PM Exposure Studies

Longitudinal PM exposure studies have been conducted in eight U.S. cities (Boston, MA; Los Angeles, CA; Baltimore, MD; Research Triangle Park, NC; Seattle, WA; Fresno, CA; New York, NY; and Atlanta, GA) over several seasons (1). These studies are being used to investigate the influence of aerosol properties from different airsheds and seasons. Study participants were monitored over the course of 7–28 days to investigate longitudinal correlations among personal, indoor, outdoor, and ambient community measurements. The studies included several susceptible subpopulations, including the elderly and individuals with cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and asthma. Collectively, these studies generated data from more than 200 people and their residences over 2500 person-sampling days. More than 15,000 individual PM mass concentration measurements were collected, along with an equivalent amount of time-activity pattern and indoor PM source data. All of the research groups involved in this work collaborated closely in the design of field studies and shared similar sampling procedures and questionnaires in an effort to create compatible data sets.

Emphasis was first placed on defining the relationships between ambient, outdoor residential, indoor residential, and personal exposure to PM. Efforts then focused on identifying and quantifying the factors that contribute to the observed differences between individuals. Important findings can be summarized as follows:

- Personal exposure/ambient concentration ratios have substantial intra- and inter-personal variability (2, 3, 4, 5).
- Stronger personal-outdoor PM correlations exist when longitudinal (repeated measure) data are analyzed by individual, over time. Although the degree of this association varies by individual, the results suggest that, for certain individuals, ambient $PM_{2.5}$ concentrations are appropriate surrogates for exposures (1,4).

- For pooled analyses that use average exposure concentrations for multiple individuals on a single day, longitudinal correlations with the ambient site concentration are high. This suggests that for community epidemiological studies, ambient PM concentrations are appropriate surrogates for exposures despite concerns to the contrary. Associations were strongest for fine particle sulfate, next strongest for $PM_{2.5}$ mass, and less strong, but still significant, for PM_{10} mass (2, 6, 7).
- Correlations between personal exposure and ambient concentrations are high when there is limited indoor activity and few indoor sources (2).
- Personal exposures to ambient PM are not substantially different for healthy and susceptible populations (8).
- Some of the interpersonal differences in personal-ambient associations may be due to spatial variability in outdoor PM concentrations. Results suggest that for the eastern U.S., outdoor PM concentrations are fairly homogenous. In the Research Triangle Park area in North Carolina, outdoor measurements at residences generally ranged from 80 to 120% of the ambient measurement at community monitoring sites with very strong correlations ($r^2 > 0.9$). In Seattle, $PM_{2.5}$ mass concentrations showed modest, yet significant, spatial variability within a radius of 20 km of monitoring locations (9); local PM sources such as mobile source and wood burning have been theorized as influencing factors. In Fresno, correlations between the ambient monitoring site and an outdoor residential site were relatively weak ($r^2 < 0.5$), presumably due to nearby mobile sources (2, 10).
- A substantial portion of the interpersonal differences in personal-ambient associations appears to be due to the varying effects of outdoor particles on indoor environments. Building type and ventilation strongly affect the indoor penetration of ambient PM. Because people typically spend more than 90% of their time indoors, understanding particle penetration into buildings is critical to determining exposure to ambient PM. Until recently, particle penetration efficiencies were thought to be constant and were often assumed to be 100%. Results from current studies show that penetration efficiencies can vary substantially by residence and by season. For 30 residences in Seattle, the estimated mean penetration efficiency was 56±8% (5,11). In 60 Fresno apartments, the estimated mean was 25±17% in the winter and 49±38% in the spring, demonstrating the substantial effect that differences in building ventilation can have over different seasons (3, 10).

Understanding the relationship between concentrations for PM mass and gaseous co-pollutants is critical for epidemiological investigations. Ambient concentrations of PM and its gaseous co-pollutants are frequently correlated, making it difficult to determine whether observed PM-health-effect associations are confounded by these gaseous co-pollutants. Results in Baltimore demonstrated strong correlations between ambient $PM_{2.5}$ and ambient gaseous co-pollutant

concentrations (i.e., O_3, NO_2) (12). In contrast, weak correlations were found between personal $PM_{2.5}$ exposure and personal exposures to gaseous co-pollutants, suggesting that the gaseous co-pollutants are unlikely confounders of $PM_{2.5}$. Finally, strong correlations existed between personal exposures to $PM_{2.5}$ and ambient concentrations of the co-pollutants, indicating that the gaseous co-pollutants may serve as appropriate surrogates of personal $PM_{2.5}$ exposures in some cities. Collectively, results from the longitudinal exposure studies have verified that for $PM_{2.5}$ mass and sulfate, the ambient monitoring site should serve as an adequate surrogate for exposure to ambient $PM_{2.5}$ mass in community-based epidemiological studies. Differences between ambient levels and estimates of personal exposure should not change the conclusions regarding epidemiology-based health outcomes. However, because individuals are typically exposed to lower levels of ambient PM than would be predicted by community monitors, the strength of the effect may be underestimated. It is important to note that the conclusions from ORD PM exposure studies are strengthened by the amount of data that was generated for different regions of the county, different seasons, and different susceptible populations.

Controlled Experiments

In addition to field studies, carefully controlled laboratory studies have been conducted to characterize indoor sources of PM and to identify key parameters that affect the penetration of ambient PM into indoor environments. In addition to particle size, several environmental factors were found to influence infiltration. These factors included building tightness (open or closed windows, number and size of wall cracks, etc.), operation of air heating and cooling units, and outdoor wind speed (13). These empirical findings carry obvious implications for geographic and meteorologic determinants of the penetration of ambient PM. The use of windows or other climate controls, as well as the quality of construction (resulting in building tightness), should be considered as interdependent factors.

Other empirical studies have quantified the contribution to indoor $PM_{2.5}$ of indoor combustion sources, including candles (14), incense, and space heaters. Additionally, as concerns have arisen regarding a potential role for biological sources of PM in causing adverse health effects, ORD has worked to develop new methods that might aid in the quantification of these biological sources. One such method was developed to measure the concentration of nonviable bioaerosols such as molds and spores which are present in indoor environments (15).

The Stochastic Human Exposure and Dose Simulation Model

Finally, as part of the overall and interactive effort to link personal exposure to ambient PM monitors, a population exposure model called the Stochastic Human Exposure and Dose Simulation (SHEDS) Model has been developed and applied in case studies. Conclusions from these case studies indicate the following:

- Personal exposure to ambient $PM_{2.5}$ varies less across a population than direct measures of total personal exposure to $PM_{2.5}$ (i.e., exposure to non-ambient sources drives variability in personal exposure) (16).
- The air exchange rate for a given residence is a critical model parameter with a significant effect on predicted $PM_{2.5}$ exposures.
- Model predictions provided exposure results consistent with the measured personal $PM_{2.5}$ exposures and the contribution of ambient $PM_{2.5}$ to those exposure estimates (based on the data from the Raleigh/Chapel Hill, NC, longitudinal exposure study).

An important question concerns the relationship between personal exposure and the sources from which the constituents derive. The SHEDS-PM Model, a revised version of the basic SHEDS Model specifically developed to study exposure to PM, has also been incorporated into a prototype source-to-dose modeling framework that can be used to analyze the relationships between sources contributing to PM mass, ambient concentrations, personal exposures, and ultimately to PM dose. This prototype has been applied in a case study that has demonstrated the ability to link EPA's most sophisticated air quality model (Community Multiscale Air Quality, or CMAQ, Model) with the SHEDS-PM Model and a conventional lung deposition model. An epidemiological case study has also been performed and suggests that the exposures (ambient and total) modeled using the SHEDS-PM Model can be used as the exposure input to epidemiological models of health outcomes.

Programmatic Need and Relevance

The association between ambient PM concentrations and health outcomes in the population, in spite of the fact that people spend more time indoors than out, raises questions regarding exposure-response relationships. It is important to gain a fundamental understanding of how these many factors interact to define individual exposures. Concerns are more significant for potentially susceptible subpopulations who may spend even more time indoors or who may otherwise alter their exposures based on their behaviors. Even from the limited studies completed to date, it seems clear that disease state by itself is unlikely to play a major role in determining total personal exposure to PM of ambient origin−specifically the $PM_{2.5}$ fraction. Individual time-activity profiles, housing, geographical setting, climate, building construction, and other environmental factors appear to have more significant influence on personal exposure. Analysis of the results from SHEDS-PM Model case studies supports this conclusion. As the research effort continues to examine the role of specific PM constituents that may be responsible for the associations between ambient PM mass concentrations and epidemiological health effects, it becomes even more important to understand the ability of community-based measurements to accurately reflect exposures to the population.

Future Directions

Fine PM mass concentrations in indoor and personal samples appear to correlate reasonably well on average with ambient measurements. This reduces the potential for exposure misclassification when data from only a limited number of ambient PM monitors are available to represent population exposures in community time-series or long-term, cross-sectional, epidemiological studies of PM. However, even though the correlations with fine PM are good, the same conclusions regarding exposure misclassification and the potential for measurement errors may not hold for individual PM constituents. If, in fact, the toxicity of PM resides in its matrix or surface constituents (e.g., metals, a speciated organic, or other component), it will be important to ascertain whether the PM components follow the mass spatial distribution in evaluating PM health effects. It will also be important to determine the temporal distribution of these constituents as they may relate to potential sources for short-term studies. Additionally, in the context of the still substantial uncertainties regarding long-term health effects, longer time-based distributions of potentially causal constituents will be important in targeting mitigation.

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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 the Research Topic 1 agenda from mass to potentially toxic components of PM. Work efforts are directed at understanding exposures to these agents, as well as evaluating and quantifying the relationship between ambient concentrations and personal exposures. This research topic was also intended to extend exposure research beyond susceptible cohorts to the general population. The original intent of the NRC portfolio was that research would be conducted in this topic area after the toxic components of PM had been identified through toxicological and epidemiological studies. Although substantial research has been conducted to understand the mechanisms of PM toxicity and to identify causal agents, specific toxic agents have not yet been identified; rather there is evidence that health effects are associated with most of the originally hypothesized toxic agents. Further, several epidemiological studies are now showing health effects associated with PM from specific sources rather than focusing on specific components.

A new perspective has been placed on this area in response to the health research. First, exposure research on individual PM species has been initiated without waiting for definitive identification of toxic components. Studies are being performed to investigate exposure relationships for as many of the hypothesized toxic components as is feasible with current technology. Results of these exposure studies will then be used to inform health studies. Second, source apportionment techniques are being incorporated into exposure research studies in order to evaluate the ambient-personal exposure relationship for PM from various sources as well as PM species.

To date, much of the research conducted in this area has been an extension of the longitudinal PM exposure studies in which additional samples were collected for the measurement of individual species. Experience gained from the longitudinal exposure studies provides valuable information for the design of studies that will specifically address this research topic. Finally, measurement methods for many PM components have been refined or developed. These methods will allow future exposure studies to more accurately measure the PM constituents of greatest interest.

Key Uncertainties, Objectives, and Special Issues

The uncertainties associated with Research Topic 2 are very similar to those of Research Topic 1, except they apply to individual PM constituents and characteristics and to PM from specific sources. Fundamental uncertainty is associated with the distributions of exposure to these PM constituents and with whether susceptible populations are more highly exposed than the general population. A second uncertainty is the relationship between ambient site measurements and exposure for these constituents. Three specific objectives are set forth for research in Research Topic 2:

- To estimate exposure distributions of PM constituents, PM characteristics, and PM from specific sources;
- To determine if ambient measures of PM constituents, PM characteristics, and PM from specific sources can be used as appropriate surrogates of personal exposure to estimate health effects in epidemiological studies; and
- To develop the data and models that will characterize and predict human exposure to PM constituents and PM from different sources relative to that measured at ambient sites.

Again, data requirements are very high for this area. Methods must be available that minimize the burden on study participants, yet are able to measure personal exposures to a range of PM constituents and characteristics at low levels. Personal monitoring that is equivalent to monitoring at a fixed speciation site would be ideal, but this is currently not feasible. However, several innovative, sensitive, low-burden methods have been developed and are being used in conjunction with new models being developed to extend source apportionment techniques to the personal level.

Major Accomplishments

As detailed in the NRC portfolio, work in this topic area was to follow work in Research Topic 1 and to begin after specific toxic constituents were identified. Consistent with the recommended approach, focused research in this area only began in 2003; nevertheless, noteworthy progress has already been made in several areas.

Through intramural and extramural collaborations, measurement methods have been developed and refined to support exposure studies of PM components, characteristics, and PM from specific sources (1–6). A moderate-burden, multi-pollutant sampler has been developed for personal monitoring to measure various PM size fractions and gaseous co-pollutants simultaneously (7, 8). Analytical methods have been refined to quantify elemental carbon (EC) and organic carbon (OC) more accurately for personal, residential, and ambient samples. EC/OC measurements will be used for source apportionment both in ambient air and at the personal level. A new assay for methoxyphenols, as markers of lignin (biomass) combustion, has been developed (9). If successfully validated, this marker will enhance the ability to separate the influence of PM from wood smoke relative to other combustion sources. Methods for speciating organics associated with PM are being developed and refined (9). These methods will enhance the suite of chemicals that can be used for source apportionment. Finally, an ultrafine ambient PM concentrator has been developed by placing an ultrafine concentrator and the recently developed Nano Micro-Orifice Uniform Deposit Impactor (NanoMOUDI) cascade impactor in series. This technology will allow researchers to conduct chemical analysis on ultrafine particles that can then be used to identify toxic components or properties and to extend source apportionment methods to ultrafines.

Several new modeling techniques are being developed to evaluate exposure to PM constituents and PM from various sources. Positive Matrix Factorization (PMF) receptor models have been refined and are being applied to determine source contributions to indoor air and personal exposure samples (8). In addition, new models have been developed using data collected in and around Seattle to determine the influence of PM infiltration factors, seasons, and spatial and temporal variables on personal exposure to ambient PM (10). While these models were developed for PM mass, they are now being extended to EC/OC, speciated organics, and other elements (11).

Many of the samples that were collected as part of the longitudinal PM exposure studies in Research Topic 1 will be analyzed for chemical constituents including sulfate, nitrate, EC/OC, elements, and, in some cases, speciated organics. It is expected that many important findings will result from both the sample analysis and the subsequent data analysis. Preliminary results have shown that penetration efficiencies for ultrafines are very low; as a result, indoor-outdoor correlations are poor (12, 13). In another study, ultrafines, EC, NO_x, and CO were measured at several distances downwind and upwind from a southern California freeway and indicated that a defined "zone of influence" exists. Beyond this zone, ultrafine concentrations fall dramatically. Concentrations of PM (number/volume), EC, CO, and NO_x were also found to decrease exponentially with distance from the freeway (14, 15).

Finally, new studies are being planned and initiated to more fully understand and model exposures to PM constituents and PM from various sources. For example, field monitoring has been initiated in 12 southern California communities to determine seasonal profiles of polycyclic aromatic hydrocarbons (PAHs), aldehydes, and quinones. These data will be used to elucidate the seasonal characteristics of PM components, as well as the magnitude and variability in ambient concentrations as a result of mobile source emissions. Planned studies will be expanded to the general population in selected metropolitan areas, as well as to selected subpopulations. These studies will draw on the results from the longitudinal panel studies; in addition, they are expected to use the refined methods and models that have recently been developed.

Programmatic Need and Relevance

The pursuit of unresolved issues of causality relative to specific PM characteristics and constituents continues, but has gradually shifted perspective to how PM and its effects are linked to their sources. Identifying the magnitude and variability of human exposures to PM constituents and characteristics is an integral part of understanding how PM from differing sources may be linked with adverse health effects. Research Topic 1 results have demonstrated that pooled correlations between ambient concentrations and exposure are sufficiently strong to justify the use of ambient data as a surrogate

for exposure in community-based epidemiological studies which evaluate short-term effects of $PM_{2.5}$ mass. However, adequate data do not exist to demonstrate the strength of the relationship for PM constituents, PM characteristics, and PM from specific sources. Results of this research area should demonstrate whether epidemiological studies can be used to evaluate health effects for constituents, to provide models that may be used to improve the exposure estimates for epidemiological studies, and to provide data for alternative approaches for conducting risk assessments, if needed. Models generated for PM from specific sources should also be applicable to evaluating the effect of source-specific mitigation strategies.

Future Directions

To date, only a few studies have investigated short-term exposure patterns to selected potential causal agents and PM from different sources. As a result, there is insufficient information on the magnitude and variability of personal exposures to potential causal agents and even less information on the relationships between personal exposures to these PM components and measurements taken at ambient monitoring sites. This lack of data introduces substantial uncertainty into current risk assessments. As more data on PM constituents become available from monitoring efforts such as the PM Speciation Trends Network (STN), more health and epidemiological studies will be conducted in order to examine the health effects associated with exposure to these constituents. Good exposure data and models enhance the utility of these studies by refining the personal-exposure-to-source relationship relative to health outcomes.

The complexity of the PM component issue has recently brought considerable attention to the advantages of a source-attribution approach to PM personal exposure and health issues. There is an added advantage as source attribution is closely related to the regulatory need for emission inventory data and community air modeling as part of NAAQS implementation. Emission profiles and characterization, conducted in parallel with toxicological and panel studies, provide a targeted strategy with which to address both sources and source-components that contribute to PM are related to health outcomes. Coordinated exposure assessments provide further refinements that can assist OAR in its regulation of source emissions. Consequently, ORD-supported programs have begun to incorporate this conceptual approach in various panel and epidemiological studies (e.g., 16), as well as in toxicological studies (17, 18). Several abstracts utilizing these approaches are expected to appear in 2004; and it is anticipated that a substantial database will be assembled soon thereafter to assess the feasibility of this methodology in linking exposure, health, and implementation.

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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

Unlike most pollutants, ambient PM varies by chemical composition and size with changes in the particle formation processes. This leads to significant variability in PM characteristics across time and space, across source categories, and across individual sources within a single source category. Many of the major sources of PM and PM precursor gases are also distinguished by high spatial and temporal variability in the magnitude of emissions. Determining detailed particle size and composition for diverse sources, such as wildfires and other uncontrolled burning, concentrated animal feeding operations (CAFOs), on- and off-road mobile vehicles, and other dispersed sources generally requires specialized and complex measurement techniques. Routine measurement methods are usually unable to provide these data; however, these source types are estimated to be major contributors to ambient $PM_{2.5}$ concentrations and exposures.

The significant policy and regulatory implications associated with emission inventories require that inventory development be led by organizations familiar with the many nuances involved in incorporating data appropriately into regulatory decisions. Since its inception (even before the post-1997 period discussed in this report), the EPA PM Research Program, as part of its support of NAAQS implementation, consulted with OAR to ensure that its research focused on the areas of highest priority to regulatory programs. EPA's priorities have focused on source types that are estimated to make large contributions to ambient PM concentrations but that have high uncertainty in respect to mass emissions and particle characteristics. These priorities are directly in line with those identified by the NRC Committee, as well as by stakeholders in state and regional agencies: notably, area sources such as uncontrolled burning, residential wood combustion and other sources of OC and EC including on- and off-road mobile sources.

These sources are typically much more difficult to characterize than industrial sources that operate within a relatively narrow band of conditions, are fixed in location, have emission points that are well defined, and can be sampled using standard EPA methods. The sources of most interest have few, if any, of these characteristics; they, therefore, exhibit much greater uncertainty in emissions data. They also present the greatest opportunity for improvement in emission characterization and inventories. Conversely, the more conventional, stationary point sources are relatively well characterized, have a significantly lower degree of uncertainty associated with their rate and composition of emissions, and therefore need less additional research.

Special Issues, Objectives, and Key Uncertainties

One of the key challenges faced by ORD in the development and performance of its emissions-characterization research program has been balancing the requirement for an accurate mass emissions inventory for NAAQS implementation purposes with the equally important need to improve the available data on chemical speciation, size distributions, and source signatures or profiles. Source profiles are needed to improve the accuracy of air quality and source-receptor models that are used as the basis for developing strategies to comply with the PM NAAQS and to improve the data available for health studies. In practice, however, the vast majority of inventory data are generated not by EPA, but rather by state and local agencies that have limited resources (in terms of both expertise and funding) and which largely rely upon data submitted by regulated industries. Because of these limitations, EPA's approach has been to develop models, measurement approaches, devices, and information that can be used by the states to generate inventory data. In particular, ORD's research efforts have focused on developing measurements and methods for source types that are the most difficult to measure and for areas where the existing data are highly uncertain.

Major Accomplishments

At the outset of EPA's PM Research Program, much of the available PM characterization data had been developed for other purposes, such as the Air Toxics Program, and was therefore focused on characteristics that were not immediately relevant to PM. The approaches used in these earlier efforts required adaptation before they could be applied to the specific needs associated with PM. Specifically, earlier particle characterization focused on inorganic compounds and did not account for particles formed from organic compounds that were in the vapor phase in the stack but condensed to form particles at ambient conditions.

NRC Committee Recommendation: Establish Standard Source-Test Methods for Measurement of Particle Size and Chemical Composition

In response to this recommendation, ORD has developed new or modified existing measurement approaches to characterize PM source emissions. These include a state-of-the-art dilution source-sampling system that can collect and measure both organic and inorganic PM constituents essential to detailed source chemical profiles. In addition to hardware development, ORD has also continued to refine procedures for applications of this instrument. Similarly, improved analytical methods are being developed to allow others to search for unique marker compounds that can be used to identify source types contributing to ambient samples. These efforts have not only generated improved source emissions data for a limited number of sources, but have also resulted in tools that can be applied to a broad range of source types. This work has provided a solid technical foundation for OAR's development of a future dilution-based regulatory measurement method for $PM_{2.5}$.

New methods for characterization of exhaust emission from heavy-duty diesel trucks during highway operation have also been an important ORD effort (1, 2). These efforts have not only improved the technologies for mobile-source emission measurement; they have also provided valuable data concerning how particle emissions and characteristics change with changes in real-world engine operation. Additional measurements of PM in exhaust plumes have provided data on how these particle characteristics change as they are diluted with ambient air, thus providing a link between stack emissions measurements and ambient PM characteristics.

NRC Committee Recommendation: Characterize Primary Particle Size and Composition of Emissions

ORD scientists collected data to improve mass emission factors as well as PM composition and size information during their work on source testing methods. Using the dilution sampling system discussed above, ORD investigators generated particle size distributions and chemical composition data for residential wood combustion, a heavy-duty diesel truck, an industrial oil-fired boiler, an industrial wood-fired boiler (3), open biomass burning, a hogged wood-waste industrial boiler, a Kraft recovery boiler, and a smelt tank vent. In several of these tests, other data were collected to characterize the performance of pollution controls (residential wood combustion) or other sampling systems (heavy-duty diesel trucks). When possible, process data were also collected to allow development of emission factors and to evaluate variability in PM characteristics with changes in process parameters.

These tests were designed primarily to evaluate the performance of the dilution sampling system under different test conditions and to provide samples for detailed analysis with the goal of identifying unique marker compounds. Even so, the data collected improve the existing source profile data and are to be included in the Agency's source profile database. In areas in which considerable research was being conducted by industry or other research organizations, ORD focused on aspects that are often overlooked but that are important to OAR or the states. For instance, one of ORD's studies of emissions from heavy-duty diesel trucks evaluated emissions during engine idling, which can be important near truck stops when drivers keep their engines running while operating air conditioners and other accessories (4). Another test examined the effects of fuel composition on the potential for emissions of particles containing chlorinated dioxins and furans (5).

In general, ORD's research efforts have gone well beyond simply measuring emission rates and PM characteristics. A series of tests on residential wood combustion equipment evaluated the ability of system design features to reduce emissions following several years of operation in private households (6) and provided data on mass emissions and organic speciation of the PM emissions as well (7). These tests generated basic data on emission rates and composition and provided a look at how well wood stove design features worked after use under real-world conditions.

Similarly, tests of open biomass burning examined not only emission rates, but also sought to identify potential marker compounds that could be used in source-receptor models to quantify the contribution of specific open biomass burning activities to ambient PM concentrations. ORD's work has identified different organic marker species associated with different types of biomass ground cover, which will allow these approaches to be used in various locations where there are disparate mixes of vegetation cover (8). Several of these tests were conducted in ORD's open-burning test facility. This approach can be used for a variety of open-burning issues regarding PM and other air quality research. Even with this facility, it is often more appropriate to conduct testing in the field, as in a series of agricultural open-burning tests conducted with EPA Region 10 and the State of Washington. One advantage of these cooperative testing ventures is that state regulators can be provided guidance in identifying conditions under which agricultural open-burning may need to be restricted.

ORD scientists also conducted a series of tests to examine the mechanisms involved in the generation of PM formed by the combustion of heavy fuel oil and pulverized coal. This work resulted in the identification of a previously unreported peak in the size distribution of coal-generated emission PM (9) and demonstrated a link between combustion system design and characteristics of particles formed from heavy fuel oil combustion (10). In addition to the particle characterization work, this research also provided the basis for a collaborative effort to link health effects with particles from specific sources through a joint research project between NRMRL and NHEERL. The techniques developed during this collaboration have now been adopted for future direct inhalation studies of emissions from a broad range of sources with the goal of linking source profiles to ambient PM toxicological studies in both humans and test animals.

While the programmatic focus of emission studies generally falls to the in-house program due to the more immediately applicable nature of the work, significant contributions to this area have also been achieved by STAR Program grant recipients. To identify unique tracer compounds, researchers produced numerous research articles characterizing organic compounds generated by the combustion of different types of biomass under different conditions (11, 12). These data will be used along with the emission data from the in-house program to update EPA's database of source chemical profiles and will therefore be available to other researchers and regulatory agencies. Together with studies of biogenic emissions by the ORD in-house program (13), these data improve the accuracy of atmospheric models of secondary pollutant formation by more accurately quantifying emissions of PM precursors. The improved emissions databases will allow these compounds to be appropriately represented in air quality models, resulting in more accurate predictions of air quality and in strategies to reduce ambient PM concentrations.

ORD also has conducted a series of tests to quantify fugitive dust emissions from construction activities. These tests have provided improved estimates of these emissions and have provided guidance to others concerning approaches for measuring these types of fugitive emissions (14).

NRC Committee Recommendation: Develop New Measurement Methods and Use Data to Characterize Sources of Gas-Phase Ammonia and Semivolatile Organic Vapors

ORD has focused much of its efforts on developing measurement methods that can be used for a range of different sources and PM constituents and precursors. One example is an open path method using a Fourier transform infrared (FTIR) system to measure ammonia emissions from hog barns and lagoons (15, 16)—sources for which traditional stack sampling methods are difficult, if not impossible, to apply. This approach can be used for other compounds, including methane and other light organics and can be applied to numerous other sources that do not have discrete stacks. This open path technique is being considered as an acceptable alternative to existing EPA methods for these emission estimates. Ammonia is of particular interest because it has such an intimate role in PM formation when coupled with acidic vapors, PM emission, or photochemical formation, making accurate emission inventories critical inputs to air quality models used by states and OAR to develop and review SIPs. Thus, the emphasis on ammonia sources has extended to research being conducted by STAR Program grantees as well. The STAR studies have generally focused on agricultural activities such as fertilizer application that contribute significantly to overall emission rates (17).

In addition to developing measurement techniques, ORD's research on ammonia emissions has also studied the most effective parameter to which the emissions can be correlated to improve estimations for model use. When developing emission inventories, activity data are as important as emissions data; and identifying the parameter that most closely tracks changes in emissions can significantly improve emission inventories. In the case of swine, animal age (closely correlated with size) and number were found to be the parameters most closely associated with emissions.

NRC Committee Recommendation: Translate New Source-Test Procedures and Source-Test Data into Comprehensive National Emission Inventories

Although OAR and state air management agencies are responsible for the development of emission inventories, ORD's research has provided significant direct and indirect benefits to the complex process of estimating national emissions of PM and PM precursors from the wide variety of sources present across the country. Directly, ORD has provided updated emission factors and improved speciation and size distribution data. Indirectly, ORD has provided expert guidance to OAR's data collection and reduction efforts. The PM implementation research management structure, formally adopted following NRC Committee recommendations, has ensured that OAR is aware of new data and methods related to emission rates and characteristics and that ORD is aware of the data

needs of OAR and, through OAR, and regional, state, and local regulatory agencies. Thus, as new information is generated it is more quickly incorporated into the inventory development process, resulting in improved emission inventories and, subsequently, improved air quality models and implementation strategies.

For the 2002 and subsequent emission inventories prepared by state agencies and OAR, the data collected using dilution sampling methods will reduce the uncertainty associated with both mass emissions and the $PM_{10}/PM_{2.5}$ split for many source types. These data will also be available for use by source apportionment modelers and health effects researchers via EPA's SPECIATE Database. Efforts continue to ensure that source and ambient samples are analyzed using compatible methods so that these data remain useful for as long a period as possible.

Additional Research: Evaluation of PM and PM-Precursor Control Technology Performance

Although control technologies were not addressed by the NRC Committee report, ORD has evaluated the performance of technologies to control PM and PM precursors to support the implementation of regulatory strategies to achieve the NAAQS. ORD has partnered with several other organizations, including EPRI and the Tennessee Valley Authority (TVA), to leverage resources and share expertise in the area of advanced PM control technologies.

Research has been conducted and is continuing to evaluate hybrid systems to improve capture of fine PM from coal-fired power plants. By applying an electric field to a conventional baghouse, an electrostatically enhanced fabric filter (ESFF) system has been developed that combines the low pressure drop of an electrostatic precipitator (ESP) and the high collection efficiency of a fabric filter to improve reduction levels at coal-fired power plants. The ESFF concept can be retrofit to plants using an ESP or fabric filter system and provides a cost-effective approach to incremental PM reductions (18).

Work is also proceeding to address a potential problem associated with the installation of technologies to reduce emissions of the major PM precursors, SO_2 and NO_x, from coal-fired power plants. In a limited number of cases, installation of wet flue gas desulfurization (FGD) in combination with selective catalytic reduction (SCR) for NO_x control can result in the formation of visible plumes of acid aerosols, resulting in potentially high concentrations of acidic PM closely downwind of plants and in noncompliance with local plume opacity regulations. A review of current literature and available data has been conducted, and measurements at pilot- and full-scale units are underway to more accurately quantify the conditions leading to these plumes.

Programmatic Need and Relevance

The ORD research efforts invested to inventory and characterize various emission sources are integral to the Agency's mandate to implement the NAAQS. As the states prepare their SIPs, they require a sound knowledge of a spectrum of emission rates associated with the sources relevant to their airsheds. These data are essential for improving the accuracy of air quality model predictions that are used to estimate the effects of compliance strategies. With the 2004 deadlines for OAR's attainment designation for the states and with the initial submission of SIPs in 2005, ORD, in collaboration with OAR, has made substantial progress in compiling data on conventional (industrial) and less conventional (agricultural) emission sources, as well as profiling characterization in order to promote more accurate airshed emission estimates in the models. More accurate and more detailed emissions data for sources with and without controls not only improve OAR's near-term ability to achieve PM reductions, but also provide the foundation for building the links between sources and adverse health effects that may allow source-specific reductions to reduce the risks associated with exposure to ambient PM. In the end, these data are a cornerstone of the regulatory process and remain a major focus of EPA's PM Research Program.

Work will continue to evaluate the effectiveness and potential side effects of control technology installation and operation to ensure that measures taken to reduce ambient PM are not causing adverse environmental effects in other ways. Future work will examine the effects of conventional PM precursor control technologies such as FGD on emissions of other pollutants such as mercury and will evaluate the effectiveness and applicability of novel approaches such as ESFF and multipollutant control methods.

Future Activities

The key areas of concern for ORD's future PM emissions characterization research program lie in two areas: carbonaceous particles and emissions from dispersed (area and mobile) sources. In both areas, ORD's efforts will focus on providing information to quantify the rates and characteristics of emissions and the variability in those measures. Carbonaceous PM is composed of a large variety of compounds from a wide range of combustion sources and will make up the majority of ambient PM following reductions from currently planned control strategies. The role of carbonaceous PM in other air quality issues, including climate change, persistent organic pollutants, and air toxics, provides additional justification for this research direction and results in more cost-effective research. ORD's current research forms an excellent basis for future progress in this area. Measuring emissions from dispersed sources remains an area in which improvements in techniques can significantly improve the accuracy of existing emissions estimates. Emissions from on- and off-road mobile sources and uncontrolled burning represent significant fractions of current carbonaceous PM emissions. Improving the accuracy of emissions estimates and speciation data can lead to more effective controls of those source types and to reduced exposure to carbonaceous PM.

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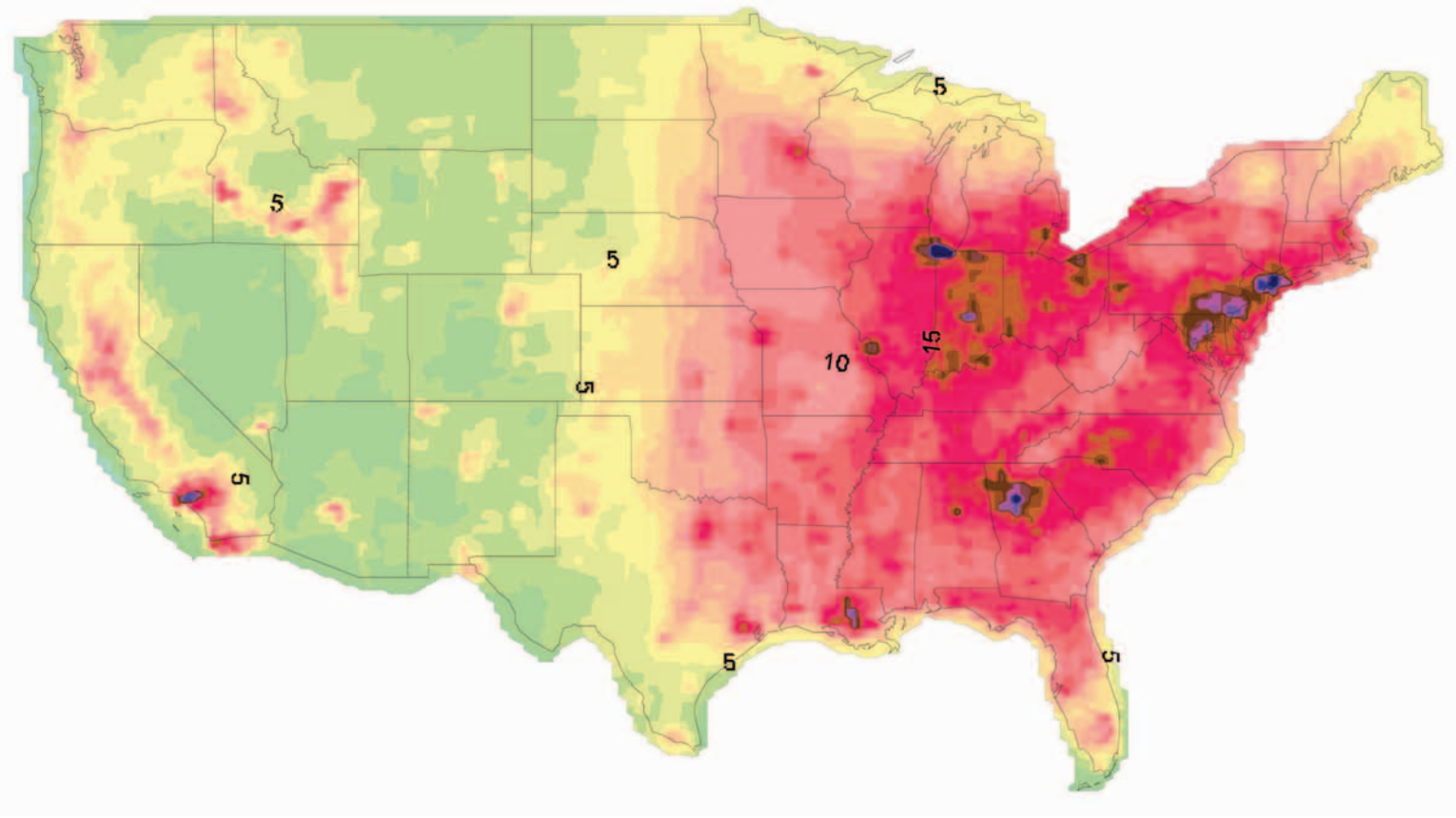

The CMAQ modeling system contains three types of modeling components: a meteorological modeling system for the description of atmospheric states and motions, emission models for man-made and natural emissions that are injected into the atmosphere, and a chemistry-transport modeling system for simulation of the chemical transformation and fate.

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

This research topic focuses on the development and testing of source- and receptor-oriented models that characterize the linkages between emission sources and ambient concentrations of PM. Source-oriented models use emission-inventory data as input and similarly incorporate meteorological and atmospheric chemistry processes to provide estimates of ambient PM concentrations. For these source-oriented models to represent the complex atmospheric chemical and physical processes credibly, it is essential to understand fundamental atmospheric chemistry and how various emissions into the atmosphere modulates these processes. Receptor-oriented models, on the other hand, use ambient air quality data to arrive at quantitative estimates of the contributions of the underlying sources to the PM burden.

Understanding the relationships between emission sources and ambient concentrations of PM requires progress in both source- and receptor-oriented models. Source-oriented models predict airborne PM concentrations by simulating chemical and physical processes that are coupled with emissions data. Receptor-oriented models estimate source contribution to airborne PM through linking emission source profiles and ambient measurements, but are not predictive. This perceived weakness of receptor models is balanced by their advantage of not requiring detailed emissions inventory and meteorological data, which are frequently uncertain or difficult to obtain. Another advantage and complementary aspect of receptor-oriented modeling is that it provides checks on the emissions inventories utilized in the source models. Thus, when used together, source- and receptor-oriented models provide EPA policymakers and states with the data necessary to develop effective mitigation strategies through predictive and evaluative capabilities.

Key Uncertainties and Special Issues

Source-oriented models for PM are continually being refined. Models improve as emission inventory data are expanded and as chemical process models are developed to characterize and predict atmospheric transformation processes affecting the size distribution and chemical composition of ambient PM levels. Evaluation is, of course, critical to these models if they are to be used for regulatory purposes and if model performance is to be improved. Such evaluations rely upon data as they become available. By 2004, EPA had accumulated $PM_{2.5}$ data (including speciated data) from its various monitoring sites over the preceding three years, thus making available ambient data against which these models could be tested and improved. At present, the models appear to provide accurate estimates of some PM products (e.g., sulfates), but fall short for others (notably nitrogen compounds such as ammonia and nitrates and organic aerosols).

Part of the problem with current model estimates of ammonia and nitrates could result from uncertainties in the emission inventory. One approach to addressing this issue which blends available ambient measurements with source-oriented model results is "inverse modeling." This approach can be used to evaluate the expected contribution of specific emmissions if ambient concentrations and other emmissions are known. In one case, inverse modeling was used to estimate emissions of ammonia and their contributions to the formation of secondary PM. While verification is needed before the results of this inverse technique can be used to adjust the emissions inventories of ammonia, the approach is promising and may be applied to other forms of PM such as OC. This issue is currently of particular interest because inventory data showing seasonal ammonia contributions are viewed as critically important to the utility of the source models in the next round of attainment determinations. Thus, more work is needed to acquire such emmissions data and to incorporate these data into the existing models to allow evaluation against the new $PM_{2.5}$ monitering. For organic aerosols, there are also potential issues related to the emission inventory, including improved accounting for sources of primary OC like wildfires. In addition, a better understanding of the processes and precursors that affect secondary organic aerosol formation is needed to improve model performance.

At best, any receptor-oriented model can only approximate the complex physical reality of the emission source. The uncertainty associated with this situation is best evaluated by examining the degree of consistency of results from more than one receptor-oriented model and by comparing results to source-oriented models. This approach is ongoing in the current EPA PM-receptor modeling-development program. Receptor-oriented models are also limited in their ability to provide accurate results in applications in which secondary products are involved. Often such models can identify the presence of secondary contributions and estimate their magnitudes, but are less successful in determining the sources of their precursor emissions. A more satisfactory solution of this problem requires combining a receptor-oriented model with additional information, such as the atmospheric processes that result in secondary formation of PM. This is referred to as "hybrid receptor modeling" and is a frontier research area.

Major Accomplishments

Source-Oriented Models

Predictive air quality models have long been of interest to ORD in its support of OAR activities. Prior to 1997, ORD modeling efforts were focused on the issues of acid deposition and oxidants. With the re-emphasis on PM in 1997 and the realization that atmospheric processes relating to PM were highly complex and involved multiple pollutants, these models were integrated and updated to provide a basis for regional and community airshed atmospheric predictions. In 1998, ORD publicly released the initial version of the CMAQ model. This model was designed to simulate the chemical and physical processes important to air quality from a "one atmosphere," multi-pollutant approach that included PM, ozone and photochemical oxidants, acid deposition, visibility, and several air toxics.

The aerosol-capable version of the CMAQ model, which was released in June 2002, was designed to provide an efficient and economical depiction of aerosol dynamics in the atmosphere. It characterizes the atmospheric PM size subdistributions, called modes (1), and simulates the processes of coagulation, particle growth by the addition of mass, and new particle formation. The model also considers both $PM_{2.5}$ and PM_{10} and utilizes estimates of the primary emissions of oxides of sulfur (SO_x), and nitrogen (NO_x), ammonia, EC and OC, dust, and "other species." This underscores the need for improved inventory estimates for ammonia and carbon to validate and refine the model. Secondary species concentrations estimated by the model are sulfate, nitrate, ammonium, water, and secondary organics from precursors of anthropogenic and biogenic origin. Extinction of visible light by aerosols is represented by two methods: a parametric approximation to Mie extinction and an empirical approach based upon field data. Also included in the CMAQ model are links between aerosols and gas-phase chemistry, aqueous chemistry (cloud processing of aerosols), size-dependent dry deposition and plume-in-grid treatments. This model is among the first to attempt to view the atmosphere in as integrated a fashion as possible with the goal of providing a credible foundation for air quality predictions that could be relied upon by OAR and state regulators.

The intent of the CMAQ model is to provide a flexible model that supports new developments by the air quality modeling community. In this spirit, several researchers funded through STAR Program grants have contributed to the current version. Two examples of this are the Sparse-Matrix, Vectorized Gear Code (SMVGEAR) (2) which numerically solves systems of chemical reactions and ISORROPIA (3) a computationally efficient but rigorous thermodynamic module that has been incorporated to refine aerosol predictions.

ORD investigators have performed an initial evaluation of the CMAQ model aerosol component to test its ability to simulate observed visibility indices and aerosol species concentrations for two summertime simulation periods (4). The visibility evaluation demonstrated that the CMAQ model reasonably captured the general spatial and temporal patterns of visibility degradation, including major gradients, maxima, and minima, but also showed that it under-predicted visibility degradation (i.e., over-predicted visibility). The speciated aerosol evaluation revealed that the model consistently under-predicted aerosol concentrations of nitrate, $PM_{2.5}$, PM_{10}, and OC. Sulfate was simulated best by the model, followed by $PM_{2.5}$, OC, PM_{10}, and nitrate.

Through collaboration with the Sandia National Laboratories, the processing speed of the CMAQ model has increased significantly with the 2003 release. As a result, the model has been used for the first time to simulate annual PM concentrations over the entire continental US for 2001. The results of this simulation were evaluated against observations from the CASTNET, IMPROVE, and STN monitoring networks and showed that CMAQ performed well in predicting monthly averages of fine particles, sulfates, and nitrates, but less well in predicting carbonaceous PM concentrations. The results of this evaluation also provided important insights regarding model performance that will be used to improve future versions of the model.

In support of the work using the CMAQ model, the STAR Program funded the following research and development for PM-source-oriented modeling.

- The Southern Center for the Integrated Study of Secondary Air Pollutants (SCISSAP) developed and evaluated a regional-scale air quality model (URM-1ATM) (6). This model played a critical role in the Southern Appalachian Mountains Initiative (SAMI) to address specific policy questions, and many of the critical components of the model are now being adapted for use in the CMAQ modeling system. Results indicate that strategies to reduce NO_x and SO_2 simultaneously will be effective in reducing ozone and PM.
- The Research Consortium on Ozone and Fine Particle Formation, the Center for Airborne Organics, and individual STAR Program grants advanced EPA's understanding of the size distribution and chemical composition of $PM_{2.5}$ and of the linkages between ozone and PM (7). Advances include tools to simulate the sources of particle emission, the modification of these primary particles over time in the atmosphere, and the formation of secondary aerosols (8, 9). Significant progress has been made in measuring the size and chemical composition of single particles using time-of-flight mass spectrometry (TOFMS) (10, 11), including the first attempts at validating advanced air quality models with single-particle TOFMS data (12). Parameterizations to simulate secondary organic aerosol (SOA) formation have been, and continue to be, a priority research area (13–15).

Receptor-Oriented Models

A principal goal of the EPA PM Research Program over the past several years has been to make "official," standardized EPA versions of popular receptor models available for state and local air pollution authorities' use in the next cycle of SIP development (beginning in the 2004-2005 timeframe). Thus, the focus has been more on model development. The two models that have received the most attention from EPA are the Chemical Mass Balance (CMB) and the Unmix models. Both are PC-based software modules, but otherwise are very different. In addition, ORD has undertaken various case studies in U.S. airsheds of particular interest as examples of how the models might be used, and, at the same time, to identify errors and inadequacies in the models.

The CMB Model (EPA CMB8.2) is a Microsoft Windows update of widely-used software that has been supported by EPA for well over a decade. The main goals of the work to update this model are ease of use and performance stability. Application of the CMB Model requires a library of source profiles that has been maintained by EPA under the name SPECIATE. The outdated nature of the SPECIATE profiles is well-recognized, and a major expansion and update of this library began in 2003 under the oversight of a newly formed workgroup that includes both EPA and non-EPA advisors. A new CMB Model was also completed, externally tested, and documented in 2003.

The Unmix Model (EPA Unmix2.3) is multivariate in nature and substantially more complicated than the CMB Model in terms of both its mathematical content and its application. Its appeal is that external source profiles are not required; instead, they are generated internally from the ambient data themselves. A case study representing the first application of this model to an urban airshed (Phoenix) has recently been completed (16). A noteworthy result was the quantitative estimation of the separate contributions of diesel and gasoline engines to ambient levels of $PM_{2.5}$. The finding that the gasoline engine contribution appearing larger than the diesel contribution contrasts with most previously published studies. In general, the Unmix Model results compared well with those of a previous analysis using another advanced receptor model, the PMF Model, which is also multivariate in nature. The chemical species that were available for this analysis are the same as those being collected in EPA's national $PM_{2.5}$ STN, which bodes well for the Unmix Model being able to deal with the vast amount of data being generated by this network. In view of the current controversy over the relative importance of diesel and gasoline engines as sources of $PM_{2.5}$, the Phoenix analysis outcome is an important contribution. The Unmix Model software has recently undergone testing and evaluation by several independent users and is now available as an EPA-supported tool.

An additional receptor modeling approach based on radiocarbon (^{14}C) measurements has been the focus of considerable EPA research for several years. Such measurements allow an estimation of the fraction of $PM_{2.5}$ carbon that is biogenic. The measurements are technologically complex, but can now be performed in an essentially routine manner. The method is being applied to samples collected during major summer field studies over the past few years in Nashville, TN; Atlanta, GA; Houston, TX; and Tampa, FL (17). A picture is emerging of a surprisingly large $PM_{2.5}$ biogenic fraction, presumably in large part from SOA resulting from the atmospheric transformation of biogenic volatile organic compounds (VOCs). This is also generally consistent with recent findings from the application of EPA's most advanced source model (CMAQ) to the Nashville airshed. Because this $PM_{2.5}$ component is essentially uncontrollable, any additional results that support this picture will have significant implications for $PM_{2.5}$ control strategies.

Atmospheric Chemistry

Efforts are underway in ORD to develop a PM chemistry model for predicting ambient compositions and concentrations of $PM_{2.5}$ containing inorganic salts and acids, liquid water, and organic compounds. Although the chemistry of inorganic compounds in $PM_{2.5}$ is relatively well-established, the development of PM organic chemistry models has only recently received attention. The first phase of the EPA program focused on SOA formation. Volatile hydrocarbons, including aromatic hydrocarbons (key constituents of automobile exhaust) (18, 19) and biogenic hydrocarbons (20, 21), undergo atmospheric transformations to form oxidation products that lead to SOA either by forming new particles or through absorption into pre-existing $PM_{2.5}$.

The overall objective of the laboratory program is to determine the key chemical and physical processes controlling the yield and chemical composition of the SOA component of $PM_{2.5}$ from atmospheric transformations of aromatic compounds, biogenic hydrocarbons, and atmospherically relevant mixtures of hydrocarbons. To address these issues, smog chamber experiments were conducted in which hydrocarbons were irradiated in the presence of NO_x to assess the effect of environmental parameters such as relative humidity on the yield and chemical composition of SOA. The hydrocarbon systems investigated were toluene, *p*-xylene, 1,3,5-trimethylbenzene, and synthetic automobile exhaust. The results of the laboratory study clearly demonstrated that aromatic compounds emitted into the atmosphere contribute to SOA formation through atmospheric transformations that form oxidation products which are partially absorbed into the organic films on pre-existing $PM_{2.5}$. The SOA yields were found to be strongly influenced by the total mass of organic compounds present on $PM_{2.5}$, but were not affected significantly by typical daytime relative humidity.

The laboratory results also demonstrated that SOA compounds from aromatic compounds are far less effective in taking up liquid water—which contributes to regional haze—than sulfate and nitrate compounds commonly found in $PM_{2.5}$. The SOA chemical composition studies are consistent with the formation of multi-functional oxygenated compounds, thus providing important tracer compounds for use in source-receptor relationships. Finally, it was demonstrated that as much as 75% of the SOA from synthetic automobile exhaust could be explained by the aromatic content of the exhaust.

Programmatic Need and Relevance

Source- and receptor-oriented models play central roles in developing, evaluating, and implementing national air pollution policies and regulations. To develop and evaluate policy decisions, source-oriented models can be used to estimate future environmental conditions by assuming alternative control scenarios. Additionally, receptor-oriented models can provide information on the sources contributing (both identification of sources and relative contributions) to air pollution problems. This information allows policymakers to develop control strategies that effectively target the most significant sources of air pollution and to better understand the potential near- and long-term effects of their decisions.

In implementing national standards such as the PM NAAQS, source- and receptor-oriented models provide states with tools to develop SIPs, which are required for regions or areas of the country that EPA determines are not in compliance with a NAAQS. In preparing SIPs, source-oriented models are used to design and evaluate alternative strategies for meeting regulatory requirements and to demonstrate that SIPs will result in the required environmental outcome. Receptor-oriented models are used by SIP developers to identify the most significant sources contributing to their air pollution problem in order to develop effectively targeted control strategies. In addition, receptor modeling provides checks on the emissions inventories utilized in the source models to develop SIPs and can be used as a tool to evaluate progress toward reaching attainment.

Future Directions

Source- and receptor-modeling tools will continue to provide information for developing effective risk management policies. Because these modeling tools represent real-world conditions, they will continue to evolve and be improved as more observational data become available and as our understanding of the complex atmospheric processes advances. Some specific areas of future emphasis for these models are listed in the following sections.

Source-Oriented Models

Development and evaluation of the CMAQ aerosol model is ongoing. Near-term efforts will focus on improving performance and predicting nitrate and organic particulates. Work is also underway to add the nucleation mode to the current version. The CMAQ model's ability to predict coarse PM will be enhanced by adding sea salt and road salt to the model. Future work also includes studies of aerosol processes in fog conditions.

Much of the upcoming effort on the CMAQ model will focus on comparing model results against data collected during field intensives (i.e., Atlanta 1999 Supersite data; Houston 2000 Southern Oxidant Study, or SOS, data; 2001 STN data; and Supersites data). The ability of the CMAQ model to predict ambient concentrations at smaller scales (e.g., at the neighborhood scale) will also be developed and evaluated. These modeling efforts will provide ambient concentration estimates that more accurately capture the spatial variability of some pollutants (e.g., certain PM constituents) and that can be used to improve human exposure estimates. Inverse modeling approaches will also continue to be explored in an effort to improve emission inventories. The CMAQ model will also be enhanced to address international transport of PM and to provide air quality forecasts of PM. Finally, in the longer term, source-oriented models will include mechanisms that treat meteorological and chemical processes simultaneously (as opposed to using separate mechanisms as in current models), allowing for more accurate treatment of the real-world interactions between meteorological and chemical process variables.

Receptor-Oriented Models

Future receptor modeling work will involve both extending current research and embarking on new initiatives. Extensions of current research include (a) adding functional enhancements to the Unmix Model; (b) concluding CMB Model development; (c) comprehensive comparison of radiocarbon measurements with concurrently measured organic species and with CMAQ model estimates of SOA; and (d) receptor model applications to additional airsheds with particular focus on the relative contributions of diesel versus gasoline engine emissions. New initiatives include (a) bringing the new PMF receptor model up to the same level of usability and documentation as the CMB and Unmix models; (b) laboratory and modeling investigation of organic molecular tracers to better distinguish types of combustion sources; (c) receptor model application to human exposure data; (d) incorporating back-trajectory analysis and atmospheric process information into receptor modeling results (i.e., hybrid receptor modeling); and (e) using receptor modeling techniques to check and improve emission inventories.

Atmospheric Chemistry

Laboratory experiments are now being complemented by computational techniques that use quantum mechanical calculations to predict thermodynamic properties that influence chemical and physical reactions in the atmosphere. Results to date using computational techniques are promising and may lead to a less resource-intensive means for filling current gaps in atmospheric chemistry and process research.

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Assessment of 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 mix of constituents derived from many sources, both natural and anthropogenic. Hence, the physicochemical composition of PM generally reflects the major contributing local and regional sources arising locally as well as regionally. Within this framework of source or origin, the nominal PM composition also varies significantly by the size mode in which it is classified (ultrafine, fine, coarse, and larger) although these three classifications are by no means homogeneous. Thus, the ambient PM mixture contains particles that can have a wide-range of physicochemical attributes and likewise can exhibit considerable size heterogeneity.

Because only a few airsheds may have a PM character representative of a single source (e.g., a smelter), a generic (and simplified) PM is typically depicted in a pie chart defining the gross composition of each PM size-mode (e.g., sulfate, nitrate, OC, EC, metals etc.) to represent all the contributing components included in any region or airshed. Therefore, studies that attempt to address the toxicity of PM for a given size mode may well face complexities that extend beyond the basic problems of dealing with mixtures. Interaction of size mode and composition provides another dimension, as does the potential for some particles within a mode or mix to be more toxic than others. In the bigger picture, assessment of the toxic nature of PM must build upon a fundamental understanding that exposure to PM constitutes an exposure to a complex mixture of PM of differing size and composition that may be chemically or toxicologically altered by the various gaseous co-pollutants that coexist in that airshed.

Key Uncertainties, Objectives, and Special Issues

A multitude of epidemiological studies has convincingly shown a positive correlation between the levels of ambient PM pollution and mortality and morbidity. To date, however, this correlation is based almost exclusively on a total mass metric—a basis which is somewhat counterintuitive given the compositional complexities of PM and the deceptively low concentrations of these constituents. Since the publication of the 1996 PM AQCD, it has been essentially confirmed that PM-related health effects are strongly associated with exposure to smaller particles that are largely derived from combustion processes. The strength of the associations are strongest for $PM_{2.5}$, then for PM_{10}, and then total suspended particulate, or TSP. The $PM_{2.5}$ fraction is largely the accumulation mode of ultrafine PM, combustion byproducts, and secondary reaction substances. It stands to reason that the contribution of any given component within the mix may not be equivalent in value or potency, but may well be highly dependent on other physicochemical attributes (e.g., co-constituents, specific bioavailability, or chelates), as well as the health status of the exposed individual. Evidence collected to date indicates that the discovery of a uniquely responsible physicochemical attribute of PM is not likely to occur.

It may be that the sources from which PM derives provide the best achievable linkages to health. Should sources or PM profiles (including sets of attributes or source attribution) ultimately emerge as causal indicators for reported effects, regulatory and risk management approaches might be targeted in a more expedient and economic manner than a mass-based standard.

To develop sound hypotheses on causality and biological plausibility, many researchers have attempted to integrate the wealth of epidemiological data with the growing body of toxicological studies to reveal coherence among the findings. In light of the difficulty of separating the physicochemical attributes of PM that may be of health significance from the mechanisms by which individual factor(s) may function in the response, a number of hypotheses have evolved espousing various PM characteristics as potentially significant contributors to the observed health effects. At present, each of the attribute-based hypotheses appears to have a sufficient database to warrant consideration and further investigation, perhaps with a source-profile focus. As the science progresses, it is important that any attribute-based hypothesis be critically evaluated and that it responds to at least the following generic questions:

- Are there environmental sources that would lead to exposure to PM with the putative constituent(s) or characteristic(s)?
- Is there evidence of personal exposure involving PM with that attribute and effect?
- Does the putative attribute possess or contribute to a toxic potential?
- Is there evidence of an exposure-response relationship, especially at the low concentrations found in the ambient environment?
- How well does the hypothesis generalize between one PM sample, exposure, or locale and another?

Major Accomplishments

Since 1997, empirical toxicological studies have provided important, but limited, evidence indicting specific PM attributes as being primarily responsible for the cardiopulmonary effects linked to ambient PM. In most cases, exposure concentrations in laboratory studies have been substantially higher than the exposures at which epidemiological studies have found effects. However, the use of higher doses in these studies does not negate their value. First of all, most laboratory studies are forced to use many fewer test subjects or animals compared to what can be studied epidemiologically. Hence, there is not the statistical power to reveal subtle, low-dose responses.

Additionally, the range of responsiveness of most study models and cohorts is likely much more narrow than the general population, especially in light of poorly understood host susceptibility factors. Thus, most of the toxicology database resides in the "Hazard-Identification" phase of the risk assessment paradigm. While signifiant uncertainty remain, sufficient coherence between the toxicological and the epidemiological data has provided a level of "biologic plausibility" to the epidemiology observation; this, in turn, has opened new avenues for investigation to link PM properties and constituents that derive from specific sources to health outcomes. The primary PM properties thought to be related to health effects are discussed in the following text.

Physicochemical Attributes of PM

Acid Aerosols

Because there is relatively little new information on the effects of acid aerosols, the basic conclusions of the 1996 PM AQCD remain unchanged. Acid aerosols have repeatedly been shown to cause little or no pulmonary dysfunction in healthy subjects, although transient slowing of mucociliary clearance has been observed after short, high-concentration exposures (~1000 $\mu g/m^3$ for 1 hour). Asthmatics, on the other hand, may experience small, variable decrements in pulmonary function during acute exposures. Linn and colleagues (2) conducted a study in which healthy children and children with allergy or asthma were exposed to sulfuric acid aerosol at lower concentrations—though still distinctly higher than typical ambient conditions (100 $\mu g/m^3$)—for 4 hours. While analysis of the entire group showed no significant effects on symptoms or pulmonary function, the allergy group did have significant acid-related increases in symptoms.

Analysis of data from Buffalo, New York City, and Philadelphia indicated that fine-mass acid sulfate was associated with increases in mortality and hospital admissions (3). Long-term exposures of animals to acid aerosols, conducted in several studies in the 1980s, did elicit some changes evident as altered airway secretory cell and epithelial number profiles and some indices of airway function; but these too were generally mild (e.g., 4). Although pulmonary effects of acid aerosols have been the subject of extensive research over many years, the cardiovascular effects of acid aerosols have received little attention. However, anecdotal reports in the personal notes of Amdur (5) from early studies of human exposure to sulfuric acid and a recent study of acidic residual oil fly ash (ROFA) PM (which also contains a considerable amount of metal sulfates) suggest the potential for cardiac function alterations which were perhaps mediated by airway responses. In the latter animal study, acidic ROFA was found to alter electrocardiogram (ECG) patterns during, but not after, the exposure (6). Thus, acid components cannot be dismissed as possible mediators of PM health effects because so little is known about potential cardiovascular effects. This hypothesis has begun to capture interest among EPA-funded programs, particularly in animal studies.

Ultrafine PM (Size, Surface Area, Number)

The physical attributes of PM−size, surface area, and number−are interrelated, descriptive metrics of PM. These properties influence PM deposition, penetration, and persistence in the lung, as well as the potential for systemic transport and the inherent toxicity of the particle itself. While a few epidemiological studies (e.g., 7) show correlations between health outcomes and ultrafine (<100 nm) ambient PM, the bulk of the information regarding the toxic potential of ultrafine particulates and the role of surface area as an alternate health-related PM metric has derived from studies of surrogate insoluble particles such as mineral oxides (e.g., TiO_2) and carbon black (8). These studies have shown that, when based on an equivalent mass, ultrafine PM can induce more lung injury than fine PM.

More recent studies in rodents appear to support the ultrafine hypothesis, showing that old age and a compromised or sensitized respiratory tract can increase susceptibility to the inflammatory effects of ultrafine PM and put the animal at higher risk of oxidative stress-induced lung injury. Results also show that ultrafine particulate effects can be significantly enhanced by a gaseous co-pollutant such as ozone (9, 10).

From a measurement standpoint, ultrafine particles pose a special problem because they have such little mass. They must be counted using special instruments (e.g., mobility shift analyzers) and may not be apparent in mass-based environmental monitoring measurements. Ultrafine particles penetrate the respiratory tract (see Research Topic 6) and deposit widely throughout the airway and lung. However, given that number rather than mass may drive the toxicity, the disproportionate number getting to the deep lung may be the key to this exposure.

As with acid aerosols, studies of ultrafine PM have focused largely on effects in the lung; but inhaled ultrafine particles may also have the potential to be distributed systemically (as discussed in Research Topic 9). The potential for such systemic transport may be dependent on particle composition (11, 12). If such transport occurs, ultrafines may have effects that are independent of the effects on the lung. Recent epidemiological studies evaluating blood viscosity as a correlate of ultrafine exposures have reported slight increases, raising the prospect of potential cardiovascular implications (7).

Fine and Coarse PM

As opposed to the ultrafine PM, the association of ambient PM_{10} and $PM_{2.5}$ with health outcomes has garnered much broader research attention. PM_{10} data collection was mandated by the 1987 PM NAAQS, and only since 1997 has more widespread measurement of $PM_{2.5}$ been initiated as a prelude to NAAQS-associated SIP development and implementation. The fine fraction ($PM_{2.5}$) comprises most of the combustion-related constituents and exhibits a complex and often variable compositional profile. Fine particles readily penetrate into the airways and deep respiratory tract. Coarse particles ($PM_{10-2.5}$)

are respirable; and, while many are retained within the nose and upper respiratory tract, they can get into the conducting and some smaller airways. However, most studies suggest minimal effects on mortality (13–16), perhaps because coarse particles are often of crustal origin

The animal toxicology also shows few effects with crustal particles (17). Considerable epidemiological evidence now generally supports the belief that $PM_{2.5}$ relates to health effects in the population better than PM_{10} or other more typically measured modes (18–20). However, studies of several morbidity end points have recently reported associations with both the fine and coarse PM fractions (14, 21). It remains to be determined whether end points are differentially responsive to these size modes.

A given mass of fine PM has a greater surface area than a comparable mass of coarse PM; likewise, there is much more surface associated with ultrafines compared to a similar mass of fine PM. The effect of size on surface area is exponential. Thus there is concern that because smaller PM fractions have a potentially enormous surface carrying capacity, this factor may relate to toxicity. As PM is a complex mixture, the potential role of surface-associated chemicals may be of considerable importance. For example, acute exposure of mice to sulfate-coated fine carbon black was found to impair alveolar macrophage phagocytosis simply based on the effective dose of sulfate that reached the macrophages compared to that by breathing a comparable level of sulfate alone (22).

Chemical Properties

Inorganic Constituents

The inorganic constituents of ambient PM derive from either natural or combustion sources. The crustal or natural constituents of PM are typically silicates that contain surface- and matrix-bound earthen metals such as calcium, magnesium, aluminum, and iron. As noted previously, most of these silicates (not being crystalline silica) do not appear to contribute much toxicity to ambient PM. Sulfate and nitrate anions derived from combustion or atmospheric processes usually combine with other constituents in PM (often water-soluble ammonium ions or organic acids, as well as elemental cations, such as first-row transition metals). The intrinsic, independent toxicities of sulfates and nitrates appear to be rather low, but they may influence the toxicity or bioavailability of other PM components. Of the cations, transition metals represent a potential class of causal constituents for PM-associated health effects that have received considerable attention. Sulfate, nitrate, ammonium, and metals make up a substantial part of the mass of ambient PM, often with a silicate or carbonaceous core, layering, or matrix. The majority of PM-associated metals in fine PM is derived from stationary or mobile combustion sources; whereas, particle sulfate, nitrate, and ammonium originate from secondary atmospheric transformation reactions involving SO_2, NO_x, and biomass ammonia emissions.

Metals

Since 1997, *in vivo* and *in vitro* studies using emission particles, such as ROFA or soluble transition metal salts, have contributed substantial new information concerning the health effects of PM-associated bioavailable metals. The metals of most interest−notably the transition metals of iron, vanadium, copper, nickel, chromium, cadmium, zinc, and arsenic−are ubiquitous constituents of PM derived from anthropogenic fossil fuel combustion. Exposure to metals seems to be widespread, as demonstrated by studies in autopsy specimens showing dramatic increases in the content of the first-row transition metals in lung tissues of Mexico City residents since the 1950s consistent with industrialization and pollution (e.g., 23). Similar studies in North America show metals in the lung tissues of urban dwellers (24)

Although there remain uncertainties concerning the differential effects of one transition metal versus another, water-soluble or bioavailable metals leached from ROFA or bulk ambient PM clearly elicit pulminary and cardiac injury in proportion to the concentration of metal in the sample (25, 26). Other studies performed *in vitro* show a similar role for metals (27–29). To date, however, only a few epidemiological studies have suggested clear role for metals in causing PM health effects (e.g., 29). The reasons for this apparent discrepancy may relate to the form or bioavailability of the metal or other confounding factors. Most of the animal studies which have examined PM-related metal toxicity involved relatively high dose instillation or inhalation exposure. This raises questions about their relevance to studies of lower concentration ambient PM. However, studies with surrogate PM of widely varying metal content (30–33) and Boston concentrated ambient particles, or CAPs, (22,34) have linked inflammatory and airway injury markers with specific metal components.

The early years of this PM initiative produced many studies showing that instilled and inhaled ROFA and related constituent metals are pro-inflammatory (cells, mediators, and molecular signaling processes *in vivo* and *in vitro*). More recently, inhaled and instilled ROFA and soluble metal components have been shown to induce cardiac arrhythmias in both healthy and diseased animal models (31, 32, 35) and to exacerbate the effects of myocardial infarction (MI) in rats (33). These studies use relatively high doses or concentrations of PM, but they demonstrate the potential for similar phenomena to occur in humans.

Of the metal-hypothesis studies relevant to the potential for human health effects, perhaps the most revealing information emerges from studies conducted with PM extracts from ambient filters from the Utah Valley. These filters were collected when a steel mill in Utah Valley closed for a labor dispute. Extracts from the PM ambient filters (containing metals and other soluble constituents) were instilled into the lungs of humans (36) and animals (37), as well as tested *in vitro* (38). These studies showed remarkable coherence with epidemiological studies of hospitalization and mortality (e.g., 39, 40) at the same time and for the same geographic area of the PM samples that were used in the laboratory studies. The response patterns in each study paralleled the metal content.

Furthermore, recent application of novel statistical approaches to the study of source-associated constituents has shown promise in linking sources with their associated emission profiles (including metals) to health outcomes in both humans (16) and animals (41). In these studies, metals are often the elemental markers for specific source types. In summary, metals appear to play a significant role in determining PM health effects; however, the issue of low dose effects and the variation in PM metal content and bioavailability remain to be resolved.

Organic Constituents and Diesel Exhaust Particles (DEPs)

Published research concerning the acute (non-cancer) effects of PM-associated OC constituents is sparse, with the exception of research specifically focused on DEPs. Like metals, organics are common constituents of combustion-generated PM and are found in ambient PM samples over a wide geographical range. OC constituents comprise a substantial portion of the mass of ambient PM (10 to 60% of the total dry mass) (42). For example, recent studies found that the average composition of ultrafine aerosols consisted of 40% organic compounds in Houston and 50% in Southern California (43).

Little is understood about the organic fraction regarding acute PM health effects. In contrast, the mutagenic (presumptive cancer) effects of ambient PM and evidence of DNA-adducts have been studied more extensively and have been linked to specific organic fractions (44). Work continues in this area, but little is directly supported by ORD. Recently, however, a re-evaluation of the ACS database of 91 U.S. cities indicated that PM was significantly linked to lung cancer outcomes over the long term (45). This cancer finding is consistent with the potential suggested in the various *in vitro* adduct and mutagenesis assays, and it may well renew interest in the carcinogenic potential of ambient PM as efforts to explore long-term health outcomes expand.

The amount of DEPs in ambient PM can vary substantially from region to region and can be very high in certain microenvironments. In Europe, DEPs are considered a major contributor to ambient PM—as much as 50% in some cases. It is also a concern in the U.S., but it is estimated that DEPs generally contribute less than 10% to the ambient. (46). The potential of DEPs to cause cancer has been well-studied, but its non-cancer health effects remain a puzzle (e.g., 47). There is, however, growing human and animal toxicological evidence that DEPs can exacerbate the allergic response to inhaled antigens (48, 49). EPA-supported research suggests that oxidative stress is a key mechanistic step in the adjuvant activity of DEPs (48, 50, 51).

One question that arises is whether the adjuvant effect of DEPs is unique. It appears that other emission PM may also have adjuvant-like activity similar to DEPs. For example, certain transition metals, such as nickel and vanadium that also induce oxidation have an analogous adjuvant effect in allergic rodents (52). As toxicological studies continue on other source-specific emissions, as well as urban CAPs, it will be important to evaluate these immunomodulating effects in the presence of allergens because this may provide insight into the incidence and severity of allergic rhinitis and asthma. A broad perspective of the carcinogenic (especially lung cancer) and non-cancer effects related to DEP exposure have been discussed in EPA's "Health Assessment Document for Diesel Engine Exhaust" (53).

The extent to which organic constituents of ambient PM contribute to adverse health effects identified by current epidemiological studies is not known. Nevertheless, organic constituents remain of concern in the context of PM health effects due in large part to the contribution of DEPs to the fine PM fraction and the health effects associated with exposure to these particles. Other carbonaceous material exists as EC, which most toxicity studies have shown to be relatively innocuous unless linked to a co-pollutant such as sulfate (54). However, epidemiology has provided limited data associating EC with mortality and adverse health on the basis that EC reflects motor vehicle contributions to PM (16).

Biogenic Constituents

Recent studies support the conclusion of the 1996 PM AQCD that primary bioaerosols at the concentrations present in the ambient environment do not likely account for the health effects of ambient PM. Ambient PM in urban air contains variable amounts of endotoxin, but the levels are typically orders of magnitude less than that needed to induce acute responses. The *in vitro* toxicological studies that have shown endotoxin associated with ambient PM to be pro-inflammatory, inducing cytokine expression in human and rat alveolar macrophages, and appear to be dose related (55, 56). Further, endotoxin content does appear to vary by size mode. Monn and Becker (57) found cytokine induction by human monocytes, a characteristic of endotoxin activity, in the coarse size fraction of outdoor PM, but not in the fine fraction. Interestingly, while studies in animal models also require more endotoxin than typically found in ambient PM to induce inflammation, recent studies suggest endotoxin may have a priming effect on PM-induced inflammatory processes (12, 58). Thus, biogenic material such as endotoxin may play a less direct role that is poorly understood. It is important to note, however, that virtually all study of so-called biogenics has been limited to endotoxins and that there remain other biologically derived materials associated with molds and fungi that are not widely studied.

Source-Specific Effects

The relationship between mortality, morbidity, and concentrations of source-specific PM is an area of increasing interest. If health effects can be linked to particular sources of air pollution, such information would prove useful for targeting control strategies. A dramatic example of the effect of control or mitigation is that of the 1990 coal ban in Dublin and the significant improvement in health as measured by population death rates. The 70% decrease in ambient black smoke levels achieved by prohibiting the use of coal in residences and businesses resulted in a 15% decrease in respiratory deaths and a 10% decrease in cardiovascular deaths (59). These findings are important because while specific components of the PM mix primarily responsible for effects were not known, there was clearly an effect.

In an analysis of the data from six U.S. cities, significant associations were found between mortality and two key sources of pollution—traffic and coal combustion—with the largest specific effect for the traffic factor (16). Others have found that combustion-related pollutants and sulfates are linked to cardiovascular mortality (60); still others have found that the fraction of PM_{10} emissions related to traffic sources is the primary driver for CVD-related hospital admissions (61).

In a study linked to one of the first Supersites, the relationship of acute cardiovascular conditions with ambient PM in Atlanta also showed that mobile source contribution appeared to play an important role (62). Yet another demonstration of the importance of local environmental sources on air quality occurred in the Pacific Northwest, where PM is seasonally dominated by wood smoke. There, investigators have been able to track the movement of wood smoke PM around the Seattle area as a step in the development studies of associated health outcomes (63). In response to the growing interest in studies which aim to attribute health effects to specific sources, EPA and the PM research centers held a workshop in the spring of 2003 to discuss methodologies and approaches for source apportionment research that can be related to health outcomes.

Programmatic Need and Relevance

The toxicological database has provided considerable evidence to support the hypothesis that certain physicochemical attributes of particles can be causally linked with regard to the observed health effects of ambient PM. A single causal attribute may not be found, but may contribute to a complex mechanism driven by the nature of a given PM and its contributing sources. The multiple interactions that may elicit a response in a host may make it difficult to identify any single causal component and may also account for the fact that mass, as the most basic metric, shows the relationships to health outcomes that it does. As research moves toward source-based linkages with hazardous components, the contributors to PM adverse health effects can be more appropriately targeted for mitigation.

Future Directions

Substantial progress has been made since 1997 in regard to PM attributes that seem to play a role in PM toxicity. At that time, it was clear that acids were a part of the story, but they were obviously not the sole factor. "Biologic plausibility" was the mantra of the skeptics who could not conceive of any component or attribute of PM that was sufficiently toxic or present in sufficient concentration to elicit the findings revealed by epidemiology. Now there seems to be little doubt that there are indeed PM-associated effects on human health at ambient levels, and several potential "active" attributes of PM seem to be involved. The large body of work on PM components has set the stage for a more comprehensive view of PM, perhaps ultimately using toxicologically profiled sources as a means to guide mitigation.

The component-focused research efforts are prepared to be integrated with the data becoming available from the speciation monitoring data from the National Monitoring Network. These monitoring programs are potential resources for source-attributed ambient PM that can be studied using a variety of toxicological tools linked to the basic knowledge of component studies and studies of emission surrogates. The critical linkages of components and sources and their toxicological outcomes can be studied with CAPs exposures, using similar study designs either in locales where CAPs units are established or at sites where speciated monitoring occurs.

When this information is tied to epidemiological and panel studies that will be conducted in the same areas, it will offer a new opportunity to investigate coherence across disciplines, allowing complementary, direct hypothesis testing and determination of mechanism. When interwoven, these approaches should provide considerable insight into the components and sources that can be linked to PM-associated heath outcomes.

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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

The most scientifically defensible relevant exposure measure for toxicity and health-risk assessment of PM is the actual dose deposition of particles in the respiratory tract and the subsequent retention and translocation of the deposited particles. However, accurate assessment of dose to the lung (and notably to a target within the lung) can be a formidable task because dose varies widely, changing with the physicochemical properties of particles themselves as well as with individual human factors such as breathing patterns and lung morphology. Moreover, the latter factors vary with age, gender, and the presence of lung disease. The presence of other pollutants also may alter the physiology of breathing. Therefore, dose information obtained from one particular subject group generally cannot always be extrapolated to other groups. Furthermore, deposition within the lung is not uniform, but varies markedly along the respiratory pathway and among different compartmental regions of the lungs. Thus, there is marked local heterogeneity of dose within the lung. In fact, the heterogeneity of dose distribution within the lung and the local enhancement can be even more exaggerated in subjects with obstructive lung diseases such as asthma and COPD. Because the translocation and removal processes of deposited particles are usually impaired in such patients, an excessive tissue burden at local sites for a prolonged period of time is a likely formula for tissue injury, disease, or other eventual adverse health outcomes. Along with exposure parameters, the internal dose is a critical factor for linking ambient air with health outcomes and for determining individual or population health risks to PM.

Key Uncertainties, Objectives, and Special Issues

Research on PM dosimetry has focused primarily on total lung deposition, but there has been less emphasis on tracheobronchial versus alveolar lung subdivisions. Most of these data have been acquired with spherical and uniformly sized particles in healthy young adult men under normal breathing conditions. While little is known about the effects of age, gender, and pre-existing lung disease, even less is known about local dose enhancement within the lung, particularly for subjects with obstructive airway disease. Data for respiratory deposition of real ambient heterogeneous aerosols are virtually non-existent. Particle dose is expressed by mass of particles, regardless of particle size, shape, chemical composition, and other particle properties that may form a more relevant dose metric to examine observed or potential health effects. In both controlled exposure and epidemiological studies, dose assessment is generally neglected because there is no straightforward way to use what is known in the context of observational or panel epidemiological studies. As animal toxicology becomes increasingly important in addressing chronic exposure, susceptibility, causality, and composition-specific effects on the lung, the links across species (especially those with impaired lungs) remain general and are of limited quantitative use in the risk assessment paradigm. This lack of information makes it difficult to extrapolate toxicological data from animals to humans and underscorees the importance of improved information on comparative dosimeter.

Major Accomplishments

ORD has made significant progress in several key areas of respiratory tract dosimetry: (a) development of a novel and non-invasive experimental method that allows the measurement of detailed regional deposition dose of inhaled particles in humans; (b) measurement of total and detailed regional deposition of fine- and coarse-mode particles in different subject groups under varying inhalation conditions; (c) measurement of respiratory dose of ultrafine particles in men and women; (d) development of a three-dimensional computer simulation model for assessing micro-dosimetry in the respiratory airways; and (e) initiation of rodent to human simulation models to mimic deposition profiles from rodents to humans.

The new method for determination of deposition profiles in humans is based upon the notion that a single inhalation of aerosol distributed throughout the tidal volume is equivalent to a series of inhalations of small volumes containing aerosol. To apply this method, the tidal volume typically is divided into 10 compartments of equal volume. Aerosol is injected as a series of small volumes during inhalation such that the series distributes within the lung. During exhalation, the distribution of the recovered aerosol can be used to calculate the deposition efficiency and deposition fraction in each of 10 compartments using software developed by ORD. Because the bolus aerosol method does not require radiolabeled aerosols, the method may be applied to a broad spectrum of subject groups, including both healthy persons and persons with lung disease. The method also allows repeated measurements in the same individuals without concerns of a potential health hazard from radioactivity. The method has been thoroughly tested and validated and has been successfully used for a variety of subjects who would be expected to have different deposition profiles. ORD's experimental dosimetry system is the only system in the world capable of such precise characterization of deposition behavior in human studies without attendant risks from radiolabeled aerosols (1,2).

Research conducted by ORD can now provide total as well as detailed regional deposition data for fine and coarse particles in four different subject groups: young adults, old adults, asthmatic subjects, and subjects with COPD (3). Men and women were studied in each group (4). Deposition dose was assessed with a variety of breathing conditions mimicking sleep, resting, and mild exercise conditions. The collective data sets are unique in their quality, size, and scope; and they provide the most accurate dose information that can be readily used for risk assessment of inhaled PM in healthy and diseased subjects (5, 6).

The hypothesis that ultrafine PM may be responsible for the observed association of health effects with ambient PM prompted ORD investigators to evaluate this unique portion of the PM spectrum. Data have been collected to determine total fractional deposition, as well as a more detailed 10-compartment regional deposition profile in adult men and women (7). This study was the first published report on the distribution of ultrafines within the lung. Somewhat surprisingly and in a manner not fully consistent with the predictions of some published models, the ultrafine PM distributed along the respiratory tract in a pattern much like that of coarse PM: bronchial airway deposition was most prominent, especially for the smallest ultrafine PM (< 20 nm). The pattern showed that, while some particles make their way to the deep lung, the majority appear to be removed higher in the respiratory tree.

ORD used data from empirical studies to develop and validate an advanced three-dimensional computer simulation model for tracking inhaled particles within the respiratory airways (8). By doing so, the exact location of particle deposition can be identified; and deposition dose can be assessed at microscopic local airway regions. This state-of-the-art technique allows respiratory dose to be estimated at specific tissue locations. The three-dimensional computer modeling of the human respiratory tract (9) was awarded the 1997 Smithsonian Award for Medicine.

In light of recent findings on cardiac and systemic effects of PM, extramural researchers have attempted to address the potential translocation of PM from the lung after exposure. The studies of deposition and toxicokinetics conducted in rodents complement and extend the perspective of the human studies and theoretical deposition models developed in-house (10, 11). These ORD studies in animal models focused on overall corporal clearance rather than mucociliary clearance *per se*. Two of the studies conducted under the auspices of the Rochester PM Research Center addressed overall clearance of ultrafine PM from the lung. Somewhat surprisingly, it was found that size alone did not dictate the translocation of similarly-sized ultrafine surrogate particles. Rather, their composition appeared to be determinant. Significant quantities of ^{14}carbon-labeled ultrafine PM translocated to the liver directly from the lung after exposure while the majority of ^{192}iridium particles were rapidly cleared tracheobronchially with only minute quantities measured in extrapulmonary tissues (12, 13).

The Rochester PM Research Center also examined deposition by PM size using controlled human exposures. In a small study of healthy and asthmatic humans, total respiratory deposition of inhaled ultrafine surrogate particles was higher compared to fine particles among healthy individuals and increased with exercise and among subjects with asthma (14). Other STAR Program researchers studied nasal deposition of fine and coarse polystyrene surrogate particles using anesthetized rats as compared to a nasal mold. Deposition fraction varied by flow rate, direction, and particle size; and comparison between the animal model and the nasal cast was favorable (15–18). Efforts using experimental data and physical concepts to develop models of particle deposition as a function of age are currently under development (19). These studies with ultrafine PM may have significant implications for the anticipated increase in diesel- and other carbon-based ultrafine PM.

Programmatic Need and Relevance

The goal of linking exposure to dose to effect remains a key objective of the ORD PM Research Program. This goal is especially applicable to the assessment of susceptible groups. Significant findings in the ORD PM Research Program indicate that enhanced dose under otherwise typical exposure conditions may occur in individuals who have pre-existing cardiopulmonary disease. Hotspots occur in the normal as well as the diseased lung due to a variety of aerodynamic factors. Hence, exposure-dose relationships must be fully understood in order to address issues of variability in healthy and diseased individuals. Salient advances in the program since 1997 include the following:

- The respiratory dose of inhaled PM is distributed unevenly within the lung, and the actual dose at local airway regions can be many times greater than the overall lung dose. The situation is particularly pronounced in patients with obstructive airway disease in whom regional lung deposition is even more highly localized.
- Respiratory dose is very comparable between young and old adults. Therefore, relative dose itself may not be a factor of concern for healthy elderly subjects.
- Although overall respiratory dose is comparable between men and women in general, women tend to receive a relatively larger dose in the upper airway regions. This may lead to somewhat different responses to inhaled PM in men and women; i.e., more upper airway irritancy in women.
- Ultrafine and coarse PM generally deposit in the same regions of the respiratory tract.
- Preliminary data suggests that some particles may, as a function of size and composition, migrate from the lung to organs and tissues.
- Risk assessment based on overall lung deposition dose alone may significantly underestimate potential risk of exposure to ambient PM, especially in diseased individuals.

Future Directions

Dosimetry research is beginning to emphasize lung deposition differences in potentially susceptible populations and in experimental animals. Currently, ORD has curtailed much of its experimental program in humans, but is planning additional work in animal models—both healthy and diseased—to support the development of predictive within-lung dose-models. Although there are limitations to the simulation of real-world situations, some work is proceeding in this area with STAR Program support while mathematical models and computer simulations are being developed to provide insights into dose distribution within the lung for a variety of subject groups. Modeling will be useful for identifying those who will be more susceptible and for determining which particular anatomic regions within the lung are most susceptible to injuries.

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VOLKSWAGEN

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?

Introduction

Air pollution is a complex mix of primary and secondary pollutants, the latter of which are generated by atmospheric transformation. While these pollutants are commonly linked to anthropogenic activities involving, among others, combustion of fossil fuels, there are various biogenic sources that significantly complicate the atmospheric chemistry. Under the CAA, air quality standards are set for individual criteria pollutants. However, ambient PM coexists with other air pollutants and, although PM often remains significantly associated with health endpoints in models that include the gaseous co-pollutants, the influence or role of the co-pollutants in these outcomes is not fully understood. It is often difficult to fully segregate the influence of individual pollutants and assess interactions; thus, the integration of observational and empirical approaches will greatly aid in the assessment of individual versus mixture risks. In addition, such work will also aid in the evaluation of the control strategies.

Our current knowledge of long-term PM effects is based on a small number of epidemiological studies that compare differences in the survival of well-characterized cohorts of human subjects with air pollution levels in their cities of residence. Such longitudinal studies are much less common than short-term time-series studies of PM due to the difficulty and expense of enrolling and maintaining follow-up of cohorts. However, as the National Monitoring Network is being revised and information is becoming available from EPA's Supersites Program and STN, the timing is right to develop both retrospective and prospective studies of mortality**,** disease initiation and progression that may be associated with long-term exposure to ambient PM mass, PM components, and co-pollutants.

Key Uncertainties, Objectives, and Special Issues

The 1996 PM AQCD concluded that PM, alone or in combination with other pollutants, was associated with a range of adverse health effects. A key uncertainty concerned the relationship between PM and co-pollutants with respect to these adverse effects, especially where PM and the co-pollutants were related to the same source types. HEI-funded re-analyses of data from time-series studies on mortality indicated that the results were little influenced by changes in statistical modeling strategies or control for weather variables, but that it could sometimes be difficult to distinguish the effects of PM from other combustion-related gaseous pollutants in data from a single city (1). The NRC Committee noted that a significant amount of epidemiological work has attempted to address this issue. However, the NRC Committee maintained that additional controlled human exposure research and toxicological studies were needed on the role of PM and gases in causing health effects, both alone and in combination, and on whether co-exposure to gases influences PM toxicity and vice versa (2).
At the time the 1996 PM AQCD was published, three epidemiological studies of long-term exposure

to PM had been published in the peer-reviewed literature. Two of these studies were geographically broad in scope: the Harvard Six-Cities Adult Cohort Study (3) and the ACS Cohort Study (4). The third study, the Seventh Day Adventist Health Study on Smog (5), focused solely on California. The first two studies reported significant associations between risk of premature mortality and long-term exposure to $PM_{2.5}$. While the California study did not find significant associations of mortality with TSP, there was a trend for respiratory cancer. These studies have been pivotal in recognizing the potential importance of long-term exposure to PM. At the same time, questions have been raised about these cohort studies, bringing up such issues as their ability to address potential confounders or effect modifiers and difficulty of retrospectively assessing exposures to pollutants using contemporary ambient monitoring data (2, 6).

Major Accomplishments

In the last five years, much of what has been learned regarding PM co-pollutant effects, confounding, and long-term risks to PM has emerged from the extramural epidemiological work conducted under the STAR, PM research center, and HEI programs. "The EPA's Particulate Matter (PM) Health Effects Research Centers Program: A Midcourse Report of Status, Progress, and Plans" provides a cohesive overview of the studies addressing co-pollutant and chronic issues (7). The advances reported are complemented by recent re-analysis efforts supported by HEI that replicated and conducted sensitivity analyses of the original results from the Harvard Six-Cities Adult Cohort Study and the ACS Cohort Study (8).

Gaseous Co-Pollutants

The NMMAPS, sponsored by HEI, included analyses of PM_{10} relationships with mortality in 90 U.S. cities with additional, more detailed analyses being conducted in a subset of the 20 largest U.S. cities (9). A uniform methodology was used to evaluate the relationship between mortality and PM_{10} for the different cities, and the results were synthesized to provide a combined estimate of effects across the cities. One key objective of the NMMAPS analysis was to characterize the effects of PM_{10} and each of the gaseous co-pollutants, alone and in combination. This assessment yielded the important finding that exposure to higher levels of ambient PM_{10} was associated with increased daily mortality rates in the 90-city analyses, and this association was not confounded by the presence of the gaseous co-pollutants (9).[1] Using an alternative method, Schwartz (11) conducted a series of multi-city analyses from 10 U.S. cities for which daily PM monitoring data were available and found consistent

[1]In further analysis of data from the 90 U.S. cities, NMMAPS investigators discovered that the default parameters within the software package commonly used for time-series epidemiological studies do not assure convergence of its iterative estimation procedure and can provide biased estimates of regression coefficients and standard errors (refer to Research Topic 10). Re-analysis of the data with more stringent parameters resulted in a smaller risk estimate, but the effect remained statistically significant; and previously drawn conclusions regarding the link between PM_{10} and mortality were still supported (10).

PM_{10}-mortality associations and O_3, CO, or SO_2. Panel studies have also begun to focus on teasing out the effects of gaseous co-pollutants as illustrated by recent cardiac studies conducted in Baltimore that included the assessment of gaseous co-pollutants (12). The analyses to assess the effects of co-pollutants have just begun and are being applied to other populations (e.g., Fresno, CA).

Recognizing the need to address the issue of co-pollutants in controlled exposure studies, ORD has initiated multiple investigations through both its intramural and extramural programs. Human studies examining the effects of CAPs exposure in different population groups have also examined ozone, NO_2, and SO_2, as well as several different components of PM (13). Analyses to segregate potential co-pollutant effects are still underway. Similarly, a number of the PM research centers and STAR Program grantees have research in progress to examine the health effects of CAPs and co-pollutants in various animal models of disease and susceptibility. To date, the bulk of the data derive from surrogate PM, products of fresh combustion, or combinations of various ROFA exposures.

One study in particular, Kodavanti et al. (14), used various ROFA samples to assess the linkages between health outcomes and ROFA composition. Specific metals display region-specific roles in the lung. On the other hand, studies nearly completed, but as yet unpublished, indicate that the effects of the PM component and the irritant gas component (SO_2) had quite distinctive regional effects. Studies with CAPs in animal models are ongoing. Some of these exposure studies are brief single exposures, while others are seasonal in design. In all cases, every effort is being made to link the responses with composition to provide potential source associations. Results of these studies are expected to begin appearing in the peer-reviewed literature within the next two to three years.

Studies on Long-Term Exposure to PM

Two critical studies have been carefully re-analyzed by independent researchers to address several concerns regarding confounding and potential bias (8). The HEI re-analysis project confirmed the results of the Harvard Six-Cities Adult Cohort and ACS studies with minor adjustments in their mortality estimates. Since the conclusion of HEI's re-analysis project, the cohorts from three longitudinal studies on PM have been extended by the original investigators to include additional years of follow up and alternative exposure measures.

Pope et al. (15) extended the original ACS study by eight years and replicated the findings of increased cardiopulmonary mortality risk, but in addition, reported a significant association with mortality from lung cancer. Although not yet published, Harvard researchers have presented findings from an additional 9 years of follow up (1990–1998) of participants in the Harvard Six-Cities Adult Cohort Study. Survival analyses of all-cause mortality showed that life expectancy continues to be reduced in the more polluted cities where the mortality risk ratios are the same as those observed

in the original study. In addition, the follow-up analyses showed that the relative risk for deaths decreased in the two cities reporting decreases in air pollution levels (16). Additionally, in the recently updated Seventh Day Adventist Health Study on Smog, investigators–using airport visibility data to estimate exposure to $PM_{2.5}$–reported increases in mortality associated with increments in $PM_{2.5}$ (17) that are consistent with other reports. Early methodological criticisms of these studies have been largely resolved, and the updated results support the concerns regarding an association between long-term exposures to PM and decreased survival (18).

Long-term exposure to PM is not only a concern for premature mortality, but for morbidity as well. Studies of chronic effects of PM exposure on the respiratory health of children have been conducted by two of the PM research centers. The Harvard Twenty-Four Cities Study assessed respiratory health and particle exposures of 13,364 fourth- and fifth-grade schoolchildren in the U.S. and Canada between 1988 and 1991. The University of Southern California Children's Health Study has similarly assessed respiratory health and particle exposures of approximately 4,000 fourth- and fifth- grade schoolchildren in 12 communities in Southern California. Recent results from this latter study associated $PM_{2.5}$ with slower growth of lung function in children residing in communities with higher than average annual $PM_{2.5}$. The slow growth appears to be nonrecoverable, and children moving to these areas also experienced slowed growth in lung function (19).

These results stimulated the Harvard and UCLA PM research centers to plan for follow-up pooled analyses of the cohorts of children from the Harvard Twenty-Four Cities Study and the University of Southern California Children's Health Study. The former study would address effects of PM attributed to power plants, while the latter would focus on PM attributed to mobile sources. Similarly, an ORD study of respiratory health in 3000 El Paso schoolchildren has been ongoing since 2000. This study assesses the effects of PM and gaseous co-pollutants (including VOCs) associated with local industry and traffic density. These data are currently being analyzed, and publications are anticipated over the next several years.

In response to the NRC Committee recommendations to begin to address long-term health effects of PM, EPA held a workshop in 1999 that explored ways to augment existing cohort studies to investigate links between long-term exposure to pollutants and cardiovascular morbidity and mortality. ORD is now funding several investigators to conduct retrospective studies using existing cohort data for such analyses. The cohorts include participants in the Nurses' Health Study and the Seventh Day Adventist Health Study on Smog.

Long-term toxicological studies in rodents have recently been initiated in an attempt to focus on the specific vulnerability of putative susceptible models and the linkages with PM composition and sources. ORD has conducted and published studies with ROFA for as long as 16 weeks; ongoing are three studies of intermittent CAPs exposure extending from 6 to 13 seasonal weeks in both normal healthy and cardiac-compromised (hypertensive) rats. The ROFA exposures induced subtle but reversible effects on blood fibrinogen and small changes in lung pathology which were highly dose and time dependent (20, 21). Perhaps most striking is the effect of the inhaled ROFA on cardiac tissue pathology, suggestive of developing injury and disease. The surprising aspect is that this type of lesion was most prominent in the healthy rats, not the compromised hypertensive rat, for reasons that are not clear (21). The data from the CAPs studies are currently undergoing analysis, but preliminary findings suggest that the daily exposure, not the cumulative (over the extended time period studied), challenge is the most important determinant of effect. The most notable outcomes thus far have been in measurements of blood fibrinogen, a finding consistent with reports in humans (13, 22).

Plans are in discussion by the NYU PM Research Center for a subchronic $PM_{2.5}$ exposure study using normal and susceptible mice. The animal models include those with both targeted mutations of the genes apolipoprotein E and the low density lipoprotein receptor and those with only the targeted mutation of the gene for apolipoprotein E. The study will use New York City CAPs and will monitor cardiac and respiratory function. While studies of this type are inherently difficult to conduct and are dependent upon the models being studied, it is expected that these studies will provide data that will be of importance to health assessments during the next few years.

Programmatic Need and Relevance

Epidemiological studies have played a critical role in previous reviews of the health-based PM NAAQS and will likely continue to do so in the ongoing PM NAAQS review. Distinguishing the effects of one pollutant from another, as well as understanding interactions between co-pollutants in producing effects, has been a key area of uncertainty in previous PM NAAQS decisions. Reducing this uncertainty will help EPA better assess risks associated with PM and other pollutants, estimate health benefits from reducing pollutant emissions, and establish the most effective and efficient NAAQS for the protection of human health

While many studies have been published on effects associated with short-term exposures, the recurring concern has been that fewer studies have assessed long-term exposures. In addition, little toxicological research has studied chronic exposures to ambient particles. In establishing NAAQS for fine particles, EPA determined that it was appropriate to rely on the annual standard as the "controlling" standard in order to reduce both short-term and long-term PM concentrations. The level of the annual $PM_{2.5}$ NAAQS was based on the results of both short-term and long-term exposures studies with greater emphasis on the results for the more numerous short-term studies. Further understanding of the role that PM and other pollutants may play in the development of disease and increased mortality risk, as well as of potential mechanisms for these effects, will assist in future decisions regarding long-term PM NAAQS.

Future Directions

The Agency has solicited proposals and expects to provide funding to recruit a new cohort in order to extend the knowledge gained from the earlier longitudinal studies. The solicitation requested proposals for prospective studies of CVD and respiratory disease endpoints in relation to PM. Outcomes of interest will include hospital admissions for CVD and respiratory disease, as well as other validated subclinical measures of the progression of CVD. The studies will evaluate alternative PM exposure metrics (mass, components, sources, and temporal patterns), the effect of PM in combination with gaseous co-pollutants, and effects on potentially susceptible groups. The new study will be able to use ambient monitoring data on $PM_{2.5}$ collected since 1999 as well as speciation site data on PM constituents. The RFA was developed in consultation with NIEHS; the National Heart, Lung, and Blood Institute; and the National Institute of Allergy and Infectious Disease.

Intramurally, EPA is collaborating with other programs, such as the National Health and Nutrition Examination Survey, to assess links between long-term PM exposure and health. These plans have been well-coordinated with the extramural program's efforts to develop the RFA for a longitudinal epidemiological study.

Animal studies are being planned to follow from the studies discussed previously. Recently there was a suggestion made to coordinate a multi-lab summer CAPs study standardizing the animal model and exposure design. The goal is to ascertain differences in the toxicity of regional PM. There may be a hiatus in the Research Triangle Park-ORD effort while the data from previous studies are evaluated and while the CAPs exposure system in the new Research Triangle Park facility is being installed and up-fitted.

This topic, perhaps more than many other research priority identified by the NRC Committee, is in its relative infancy. While the epidemiological literature continues to address the extent to which PM causes health effects independent of other pollutants, controlled exposure studies have just started to analyze this question. Similarly, given the complexity, expense, and duration of longitudinal epidemiological studies of PM health effects, coupled with the historic lack of fine PM monitoring data and adequate biomarkers, it is not surprising that such studies are only now coming into existence.

Analogous problems exist with long-term animal studies, which at present are likely to be limited to seasonal studies due to the practical limits of working with animals and compromised cohorts. One key is the linkage to the contributing sources of PM. Thus, there is a critical dependency on monitoring and analytic data collected with an eye to source apportionment analyses. The development of the National Monitoring Network will be essential to many of the planned epidemiological studies, and it is anticipated that animal studies will likewise attempt to use this rich database to assess hypothesis of causality and susceptibility.

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Susceptible Subpopulations

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

Introduction

Time-series epidemiological studies associating mortality and hospital admissions with daily ambient PM concentrations suggest that responses to PM predominate in certain subpopulations, as defined by age and pre-existing disease. Observational studies conducted in the early 1990s funded by EPA, HEI, and other sponsors have shown that people older than 65 years have higher mortality risks associated with PM exposure than the population as a whole. Likewise, individuals with pre-existing CVD or respiratory disease (including COPD and pulmonary infection) show similar or higher risk of PM-related mortality and morbidity. Asthmatics, especially children, also have been identified as a potential susceptible subpopulation based on their diary records, hospitalization, school absenteeism, and use-frequency of bronchodilators that associate with ambient PM levels. There is even limited evidence of prenatal effects of PM (and perhaps co-pollutants) on cardiac development and mortality in the first two years of life and perhaps of further suppression of lung growth during childhood.

Clearly, there is sufficient evidence to conclude that certain groups are likely to be more sensitive or responsive to PM than others. Genetic variability may influence the distribution of sensitivity, but there may be physiological susceptibility factors common to the groups that may indicate a higher risk potential. Thus, while the first step is to identify susceptible groups within the general population for inclusion into the overall risk assessment paradigm, characterizing the risk factors that underlie susceptibility may be most the most fruitful revelation in the long run.

Key Uncertainties, Objectives, and Special Issues

The 1997 NAAQS decision recognized the supportive evidence for greater risk in susceptible subpopulations. The early findings that supported the decision have since been replicated in many more observational studies. While the elderly and the very young may be somewhat more sensitive than the population in cross-section, those with impaired cardiovascular and respiratory systems appear to be at greatest risk for PM mortality and morbidity. Indeed, because these disease "entities" often involve both organ systems (by virtue of their physiological interdependence), it may be difficult to segregate organ-specific risk with standard epidemiological methods. Hence, clinical studies in human volunteers and novel animal models of disease have begun detailed examinations of the biochemical and physiological mechanisms of PM-associated risks. When combined with panel studies, it appears that the strong PM associations with the presence of pre-existing cardiopulmonary disease have been affirmed. What is left to explore is the "how" and "why." As noted previously, the CAA requires the protection of susceptible groups. As the evidence

accrues, it appears that susceptibility may be at the hub of the entire issue, at least with regard to acute effects. How susceptibility is related to long-term or chronic effects is virtually unexplored. However, regarding the issue of susceptibility in the context of the numbers of people affected, even a small percentage reduction in PM levels could translate to a large number of avoided cases.

In 1997, there were 3,475,000 U.S. hospital discharges for respiratory diseases: 38% for pneumonia, 14% for asthma, 13% for chronic bronchitis, 8% for acute bronchitis, and the remainder (27%) not specified (1). Of the 195,943 deaths recorded as caused by respiratory diseases, 44% resulted from acute infections, 10% for emphysema and bronchitis, 3% for asthma, and 42% for unspecified COPD (2). This point is even more marked among the subpopulation with CVD. For the same year, 1997, there were about 4,188,000 U.S. hospital discharges with heart disease as the primary diagnosis (1). Among these, about 2,090,000 (50%) were for ischemic heart disease; 756,000 (18%) for MI or heart attack (a subcategory of ischemic heart disease); 957,000 (23%) for congestive heart failure; and 635,000 (15%) for cardiac dysrhythmias. Deaths from heart disease in 1997 were 726,974 (2). As there were about four times as many CVD deaths when compared to those due to respiratory disease, the CVD group is clearly at higher risk of mortality overall. Moreover, there are many more people with CVD—many with a silent condition that usually goes undiagnosed until a cardiovascular event. Thus, despite the fact that the respiratory and CVD risks reported in several studies have been about equal, PM-CVD interactions are likely to outnumber the PM-respiratory events. Given these numbers, the societal economic and personal costs of PM effects to those who may be susceptible due to an underlying disease are substantial.

Major Accomplishments

Ambient PM Exacerbation of Respiratory Disease Conditions

Many time-series studies have shown that pre-existent chronic lung diseases as a group (but especially COPD) constitutes a risk factor for mortality associated with PM exposure (3). Studies with humans that might reveal more specific data have been limited by ethical exclusions of severely diseased individuals and by the absence of valid physiological indicators of subclinical disease (parallel to the function of ECGs in cardiac disease). Measures of blood-gas saturation and lung function do not appear to be sufficiently revealing or sensitive to mild physiological changes in those with moderate clinical disease.

On the other hand, subjects with moderate COPD and asthma have been exposed to inert aerosols in controlled human exposure studies to assess the distribution of PM within the lung (4). It is now clear that any disease that involves the airways elicits a heterogeneously distributed deposition of PM within the lung, as discussed in Research Topic 6. This study and subsequent models (5) have shown up to 10-fold higher than normal deposition at airway bifurcations where the creation of

"hotspots" may well have biological implications, especially if the individual already has diminished function or other disability due to the underlying disease. Thus, the dosimetry of PM within the lung must be considered an important element of the susceptibility paradigm with almost any cardiopulmonary disease condition.

There are several reports of associations between short-term fluctuations in ambient PM and day-to-day frequency of respiratory illnesses (6). In most cases, notably in pre-teen children, assessments have found exacerbation of pre-existing respiratory illness and related symptoms rather than *de novo* acute respiratory infections (7). The use of inhalers has also been shown to increase in many young asthmatics in response to air pollution in general and PM in particular.

A study of children in East Germany found that the prevalence of nonasthmatic respiratory symptoms including bronchitis, otitis media, frequent colds, and febrile infections declined between two periods in the 1990s when ambient air pollution levels declined (8). Others have observed that acute respiratory infections associated with PM exposure in elderly subjects with cardiopulmonary disease appear to result in complications of the underlying cardiac disorder and require subsequent hospitalization (9). Animals exposed to surrogate PM have not consistently exhibited vulnerability to infections, but altered lung phagocyte function has been reported (10, 11). Thus, while there appears to be a strong likelihood that infections may be worsened by exposure to PM, general statements regarding interaction of PM with response to infectious agents are difficult to validate due to the unique attributes of various infectious agents and the variability of the immune status of the host.

Researchers have designed experimental studies to elucidate aspects of the underlying biology of lung diseases that may lead to heightened sensitivity to PM (notwithstanding the dose issue noted previously). Apart from the functional linkages with the cardiac system for maintenance of adequate gas exchange and fluid balance, inflammation in the diseased respiratory tract (airways and alveoli) could also play a key role. Studies in animals genetically or exogenously altered to induce inflammation show that such animals may become intrinsically more responsive to surrogate or concentrated ambient PM (12–15). Existing basic biological data are sufficient to hypothesize that exudated fluids in airspaces may either interact differently with deposited PM to augment injury (e.g., to generate oxidants)(16, 17) or to predispose the lung (18) to enhance a response to a stereotypic PM stimulus through otherwise normal pathways. Less appreciated is the loss of reserve (functional or biochemical) when the susceptible individual is incapable of sufficient compensation (e.g., antioxidant responses)(19). Any of these or related mechanisms may contribute to susceptibility and may be one common factor that can be attributable to other susceptible groups. Understanding these factors will ultimately aid in addressing the true risk of susceptible groups to PM.

Ambient PM Exacerbation of CVD Conditions

Exacerbation of heart disease has been associated in time-series studies not only with ambient PM, but also with other combustion-related ambient pollutants such as CO and NO_2. It remains unclear whether the combustion gases in this context are acting as surrogates for PM or as additional predictors. A number of studies using creative approaches and surrogate exposures have provided additional evidence of direct cardiac effects in humans exposed to air pollution. For example, recent panel studies of human subjects with CVD have shown correlations between air pollution levels, notably levels of PM, and the frequency of intervention discharges of implanted cardiac defibrillators as well as elicitation of ST-segment depression during repeated exercise tests (20).

Analogously, Pope et al. (21) have noted altered autonomic control of cardiac function [in the form of reduced heart rate (HR) variability (HRV)] over a wide age-range of healthy subjects when they were introduced into an airport lounge with active smokers. Evidence of vascular narrowing with exposure to CAPs has also been reported suggesting parallel cardiovascular responses in human clinical studies (22). Collectively, these and previous studies that have shown ambient PM-induced alterations in cardiac physiology in human subjects (20, 23, 24) and that are complemented by animal studies (12, 25-27) provide evidence that there are significant cardiac responses to PM. Moreover, changes in plasma viscosity (28) and other factors involved in clotting function (29) provide a plausible sequence of events that could culminate in sudden cardiac events in some individuals.

The recent HEI report on an epidemiological study in Montreal provides interesting new information regarding the types of medical conditions that potentially predispose individuals to increased risk for PM-associated mortality (30). Investigators linked immediate and underlying clinical conditions recorded on the death certificate with indices of ambient PM (TSP; PM_{10}; estimated $PM_{2.5}$; coefficient of haze, or COH; sulfates; and extinction coefficients) lagged for 0 to 4 days. The results supported previous findings identifying those with pre-existing cardiopulmonary conditions at increased risk for ambient PM effects and implicated another possible risk factor, diabetes (which involves cardiovascular complications as it progresses) as a potential susceptibility condition. Zanobetti and Schwartz (31) have found more directly that those with diabetes are at increased risk; presumably, this finding is related to the cardiac and vascular complications associated with this disease. At the present time, diabetes is being investigated as a mediator of PM-related risk in epidemiological studies; parallel work is proceeding in animal models to segregate the underlying mode of action.

Age-Related At-Risk Population Groups: The Elderly and Children

The very young and the very old have been identified among those most affected by PM air pollution. As noted previously, a major factor in increased susceptibility to air pollution is the presence of a pre-existing illness as discussed by Zanobetti et al. (9). The effect of PM pollution on mortality and acute morbidity is well-documented in time-series studies: risk increases gradually above the age of 45 and continues to increase more steeply after 65 years. It is well known that cardiopulmonary diseases are more common to the elderly and are the major cause of death in older age groups.

While panel studies of PM morbidity have tended to focus on healthy people in retirement homes (23) and while chamber studies with elderly volunteers exposed to concentrated ambient PM (32) are even more restrictive regarding health exclusion criteria, these studies have shown subtle alterations of autonomic control of cardiac function (i.e., slight depression of HRV) and small changes in blood clotting factors. Though small, these changes are considered clinically significant based on studies of risk in cardiac patients and studies of CVD progression in the general population. The HRV changes contrast with the lack of similar physiological changes in healthy young people (29) who surprisingly have more consistent changes in the clotting factors. The biological significance of these results and their reproducibility remain to be explained but are the subject of continuing human and animal studies.

Chronic Exposures and Susceptibility

Susceptibility to health outcomes from long-term or lifetime exposures is poorly understood. Three longitudinal studies (two with partial funding by the EPA) have shown elevated mortality risk from chronic PM exposure (refer to Research Topic 7), but these studies were not able to reliably separate the effects of gaseous co-pollutants and other risk factors from PM. Over the long term, innate differences in metabolism or other mechanisms may affect the likelihood of progressive deterioration or disease (COPD, CVD, or lung cancer). Uncertainties remain regarding the extent to which progression is a product of total cumulative or repeated episodes or patterns of PM exposures and to what degree disease or other risk factors add to or complicate the magnitude of response.

Regarding potential lung developmental effects of PM, there exist both experimental and epidemiological data that, though limited, suggest the early post-neonatal period of lung development is a time of high susceptibility for lung damage by environmental toxicants. In experimental animals, for example, elevated neonatal susceptibility to lung-targeted toxicants has been reported at doses "well below the no-effects level for adults" (33). Furthermore, acute injury to the lung during early postnatal development may impair or retard normal repair, growth, and maturation. These and other results in animals appear to agree at least qualitatively with the recent findings for young children living in the Los Angeles area where both oxidants and high levels of PM prevail (34).

These and other types of health effects in children are emerging as potentially important issues that were not appreciated in 1997. Unfortunately, relatively little is known about the relationship of PM to these and other serious health endpoints (low birth weight, preterm birth, neonatal and infant mortality, emergency hospital admissions, and mortality in older children). The recent report (35) linking CO exposures of mothers in Los Angeles with fetal cardiac defects raises concerns about PM, which was inconclusively linked in the study. Similarly, little is yet known about involvement of PM exposure in the progression from less serious childhood conditions, such as asthma and respiratory symptoms, to more serious disease endpoints later in life.

Programmatic Need and Relevance

Studies of PM generally focus on its attributes or exposure issues. However, the collective and accumulating evidence indicates that not everyone is similarly affected by PM. There are subpopulations, generally described in the context of overall health, who appear to be susceptible and who may in fact statistically drive much or most of the overall population response. Identifying these populations and, more importantly, identifying the host characteristics that contribute to heightened risk are vital to ultimately protecting those at risk by minimizing exposure and recommending ways to minimize personal risk.

While there is some appreciation of the factors that may contribute to acute PM risk, evidence is needed to segregate which subpopulations may be more prone to adverse health risk with chronic exposure. As EPA moves toward the next cycle of the NAAQS review, this information will help support the quantification of risk for the most susceptible subpopulations.

Future Directions

Host variability is undoubtedly an important factor in determining the response profile of a population exposed to PM. Studies to date suggest that certain subpopulations are indeed more acutely responsive to PM, perhaps due to differences in lung deposition (either in terms of dose and/or intrapulmonary distribution) or to other biological aspects of the cardiopulmonary system or disease. EPA will emphasize the characterization of susceptible groups in extramurally supported epidemiological studies of health effects stemming from long-term PM exposure.

The role of innate host attributes of risk grounded in one's genetic code is largely unknown, but potentially of great importance. Changes in these attributes with age or the presence of deteriorated cardiopulmonary function contribute further to risk, but these changes are likely to be studied only in population-based analyses. Research needs to focus on individual risk and on the elements that define or underlie that risk. Both clinically based and field studies of humans will help focus attention on potential factors, but it is animal-based study that will permit specific hypothesis testing to define mechanisms.

EPA is currently expanding its knowledge base in the area of studies of susceptibility with both human clinical and animal disease and/or genetic model studies. As the mechanisms of action of cardiorespiratory response become more clear, these mechanisms can be investigated in potentially sensitive subpopulations and animal models. Similarly, the role of loss of reserve or compensatory response has not been adequately studied. Chronic disease and the process of aging erodes reserve and lowers the threshold for toxicity or response. Thus, emphasis in EPA studies will be placed on both wings of the response paradigm−induction and recovery.

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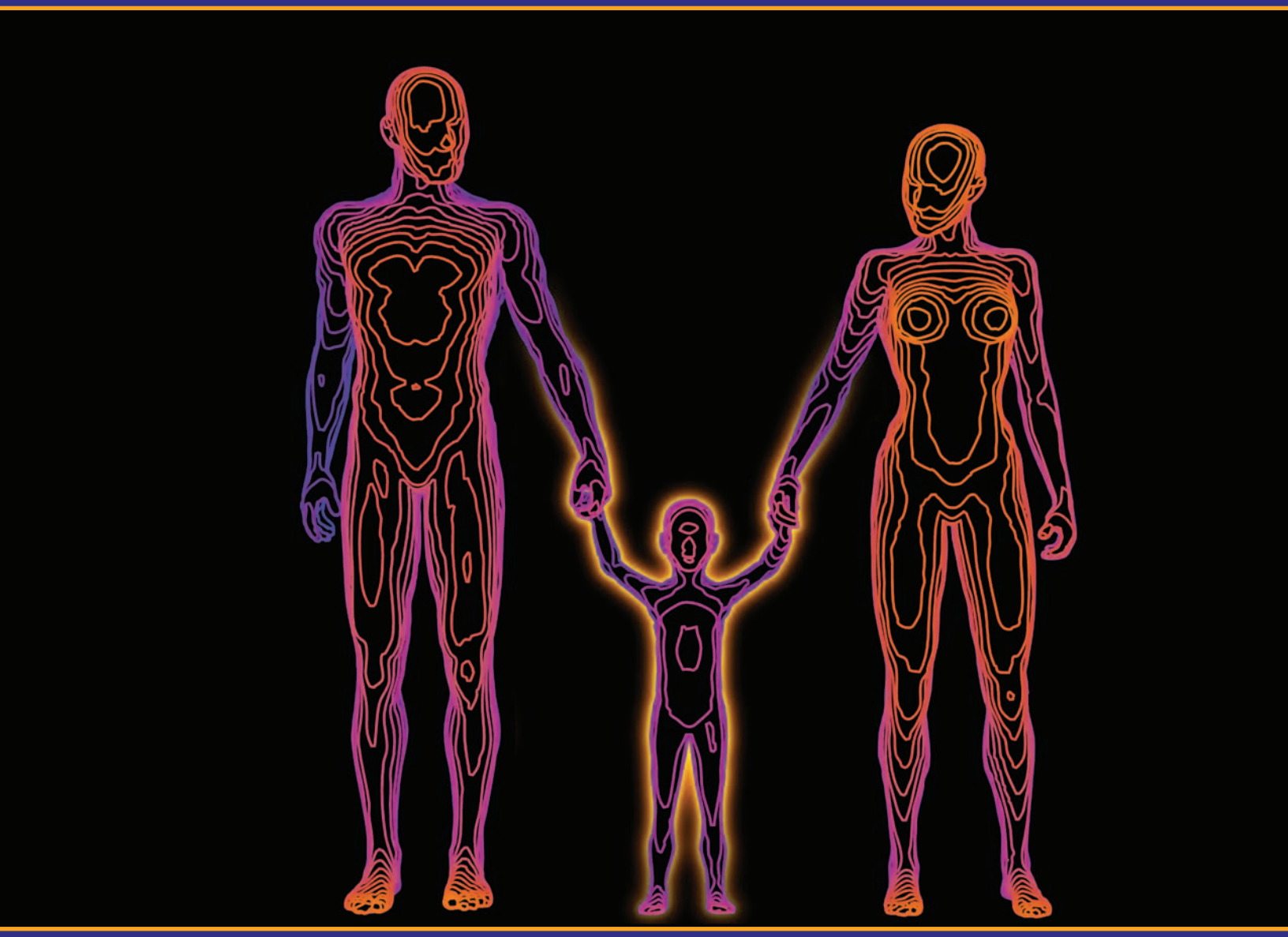


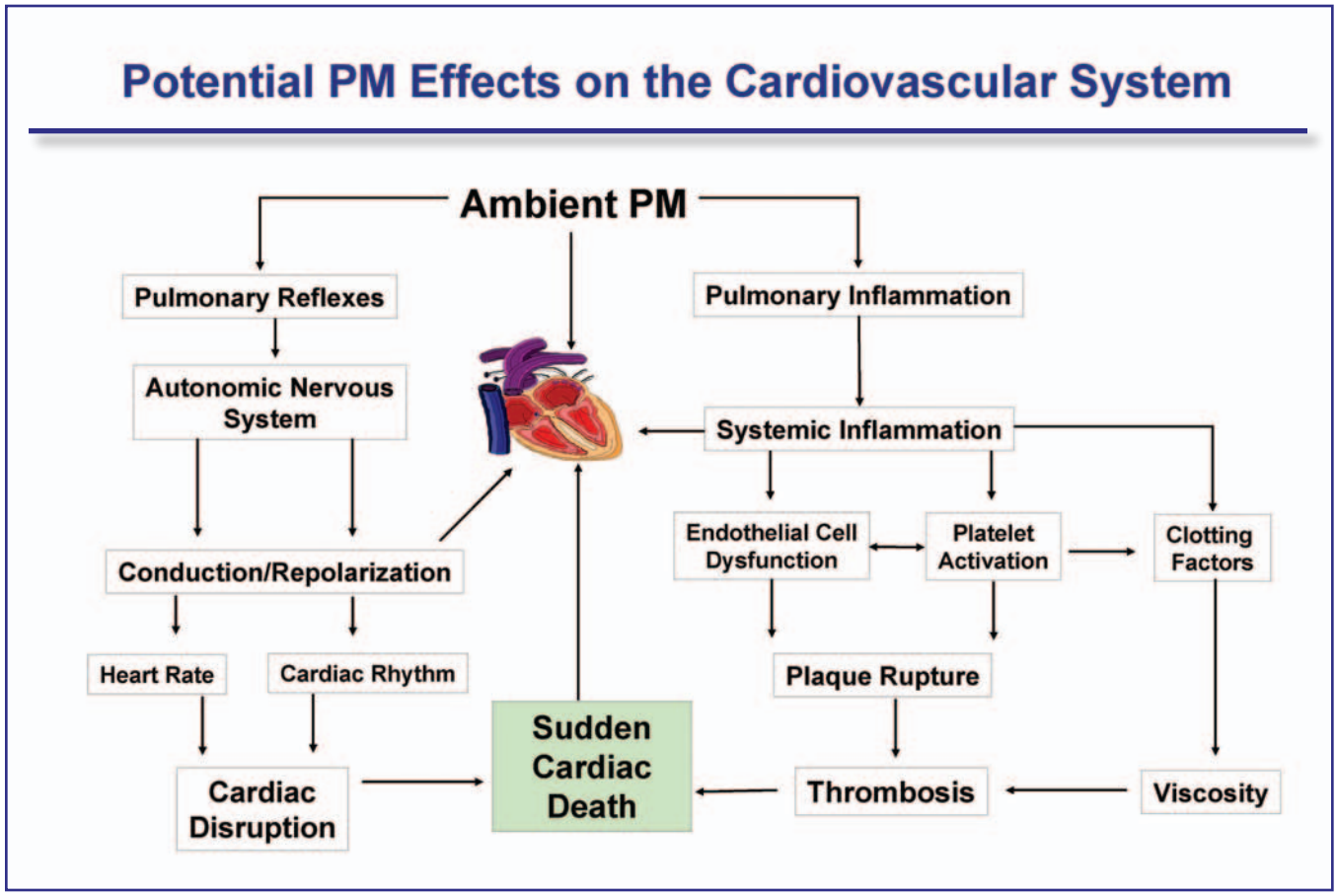
Mechanisms of Injury

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

Introduction

The recommendations for changes in the 1997 PM_{10} and $PM_{2.5}$ NAAQS were primarily based on a large and coherent epidemiological database of significant associations between ambient air PM concentrations and excess mortality and morbidity. Although the 1996 PM AQCD provided some information that lent biological plausibility to causal links between PM and health effects, evidence from controlled human and animal exposure studies was largely unavailable at that time. Based on this information gap, the NRC Committee placed a high priority on gaining a better understanding of the biological plausibility and mechanisms of PM-associated health outcomes. Since that time, significant progress has been made in identifying pathophysiological processes in humans and animals exposed to various PM. These processes can provide insight into the mechanisms by which PM may exert its effects.

Several mechanistic pathways by which PM could cause adverse health effects have been investigated. Some of them are quite complex and involve interaction between several organs or tissues (e.g., lung, heart, vascular system, autonomic nervous system). The figure below highlights the complexity and interdependency of some of these pathways.



The primary portal of entry for PM air pollution is the lung, and PM interactions with respiratory epithelium and alveolar macrophages likely mediate a wide range of pulmonary effects. These include lung injury, inflammation, and changes in resistance to infection or sensitivity to allergens. PM or its reaction products may also stimulate airway sensory nerves, leading to changes in lung function and autonomic tone. However, PM likely exerts many systemic effects, with perhaps the most significant from a health effect standpoint being those on the cardiovascular system.

There are several mechanisms by which PM may directly or indirectly affect the cardiovascular system. Potential neural mechanisms involve the autonomic nervous system (ANS) via direct pulmonary irritant reflexes or reflexes activated during pulmonary inflammation that would ultimately influence cardiac function. Ultrafine or soluble PM components may enter pulmonary capillary blood and be rapidly transported to extrapulmonary tissues, such as heart, liver, and bone marrow tissues, with either direct or indirect effects on organ function. Some of these effects could include changes in ion channel function in myocardial cells, ischemic responses of the myocardium, systemic responses including inflammation which can trigger endothelial cell dysfunction, and triggering thrombosis via alterations in the coagulation and clotting cascade.

It should also be remembered that PM is a complex mixture of many different components, and it is possible that different components may stimulate different mechanistic pathways or interact in other ways to alter response thresholds (e.g., endotoxins and other PM constituents). Thus, exposure to PM may result in one or more pathways being activated depending on the chemical and physical makeup of the PM.

Key Uncertainties, Objectives, and Special Issues

Historically, most air pollutants studied by EPA have had the respiratory system as their primary, if not only, target. However, PM, unlike other criteria pollutants, has been associated with significant acute mortality. Thus, different mechanisms likely underlie the pathophysiological events which lead to PM-induced mortality; and these events do not seem to be confined to the respiratory system. A key challenge facing EPA was the development of expertise in areas not traditionally related to air pollution research, particularly in the areas of cardiac and vascular biology. To help address these needs, EPA has sponsored or co-sponsored two workshops designed to bring cardiovascular researchers together with respiratory toxicologists who perform PM research. EPA has also focused a part of its STAR grants program on attracting researchers with cardiovascular expertise into the PM research community. In addition, ORD researchers, as well as PM research centers funded by ORD, have initiated collaborations with cardiovascular researchers.

PM-induced Inflammation

Airway injury and inflammation are well-known consequences of toxic inhalation exposures. The presence or absence of an inflammatory response is an important issue for several reasons: Inflammation may induce systemic effects, including an acute phase response with increased blood viscosity and coagulability, which have been linked to increased risk for MI in patients with severe coronary artery disease. In chronic respiratory diseases, such as asthma and COPD, inflammation is a key pathophysiological feature. Chronic, repeated inflammatory challenges of the airways may result in structural changes in the lung that can lead to irreversible lung disease. Thus, inflammation may be involved in both acute and chronic effects. Furthermore, systemic inflammation is known to contribute to a number of diseases, including CVD and diabetes. A number of EPA studies have shown that instillation or inhalation of particles causes pulmonary inflammation and epithelial injury. Many of these studies were conducted to characterize the effects of metallic PM components and are described in the section of Research Topic 5; examples of additional studies are presented in the following text.

Exposure of healthy young humans to Chapel Hill CAPs causes mild pulmonary inflammation as evidenced by increased numbers of neutrophils present in bronchoalveolar lavage fluid (1). Healthy humans exposed to Los Angeles CAPs or to carbonaceous ultrafine particles provide evidence for effects on systemic markers of inflammation and leukocyte recruitment. These studies indicate increased blood levels of soluble intercellular adhesion molecule-1 (sICAM-1), a transmembrane protein which is expressed on leukocytes and endothelial cells and which plays an important role in monocyte recruitment to atherosclerotic lesions and inflamed airways (2). These human studies were complemented by animal studies in which healthy dogs exposed to Boston CAPs showed increases in neutrophils in bronchoalveolar lavage fluid and in circulating blood neutrophils (3). However, rodent studies have not been consistent in their responses to CAPs from Research Triangle Park (4) and from New York City (5); minor changes occurred in both healthy and compromised animals.

Effect of PM on Infectivity

Epidemiological studies have demonstrated that infection, especially pneumonia, contributes substantially to the increased morbidity and mortality among elderly individuals following exposure to PM. This suggests that inhaled PM can act as an immunosuppressive factor that undermines the pulmonary immune responses of normal host. For example, exposure of bacterially infected rats to New York City CAPs altered both pulmonary and systemic immunity and exacerbated the infection process in a time-dependent manner (6). *Streptococcus pneumoniae*-infected rats exposed to PM also demonstrated increased burdens of pulmonary bacteria, numbers of circulating white blood cells, numbers of pneumococcal-associated lung lesions, and incidence of bacteremia compared to air-exposed, infected control rats. In addition, PM from various sources has been shown to induce

apoptosis in alveolar macrophages, which can lead to decreased phagocytic defenses in the lung. These findings suggest that PM exposure may affect the host immune response during pulmonary infection and may help explain epidemiological observations.

PM Affects Autonomic Control of the Heart

There is growing clinical and epidemiological evidence that ambient air pollution can precipitate acute cardiac events, such as angina pectoris, cardiac arrhythmias, and MI. A number of EPA studies have demonstrated that inhaled particles can affect the heart through the ANS. Direct input from the lungs to the ANS via pulmonary afferent fibers can affect both HR and HRV. The heart is under the constant influence of both sympathetic and parasympathetic innervation from the ANS, and monitoring changes in HR and HRV can provide insight into the balance between those two arms of the ANS. During recent decades, a large clinical database has developed that describes a significant relationship between autonomic dysfunction and sudden cardiac death. One measure of this dysfunction, low HRV, has been implicated as a predictor of increased cardiac morbidity and mortality.

Several independent epidemiological panel studies of elderly volunteers (some of whom have CVD or pulmonary disease) have reported associations between PM concentrations and various measures of HR and HRV (7–9). Although there are some differences among these studies, they generally report a negative association between PM levels and standard deviation of normal-to-normal beat intervals (SDNN), a measure of HRV found by the Framingham Heart Study to be associated with a higher risk of death. Increases in PM have also been associated with decreases in HRV in the high frequency (HF) range, which is a reflection of parasympathetic modulation of the heart. Thus, taken as a whole, evidence from panel studies indicates that PM can directly affect the ANS in such as way as to alter HR and HRV.

The reported associations between PM levels and changes in HRV in the panel studies have been confirmed in controlled exposure studies. Healthy elderly volunteers exposed to Chapel Hill CAPs experienced a decrease in the HF component of HRV while no change was observed following exposure of these subjects to clean air (10). A positive association between PM and HR has also been reported in healthy rats (11); elevated HR is known to be associated with hypertension, coronary heart disease, and death. In related animal studies, alterations in HRV have been reported in healthy dogs exposed to Boston CAPs (12). Additionally, in similar rodent studies, a model of severe lung inflammation developed increased HR following exposure to urban PM (13).

As a caution, however, it should be noted that lowered HRV has primarily been used as a predictor of subsequent increased mortality and morbidity. It is not yet clear whether a single reversible acute change in HRV places a person more at risk for an immediate adverse cardiac event. Additionally, it is not yet known whether changes in HRV associated with exposure to PM represent an independent risk or are just a marker of exposure.

PM Alters Cardiac Repolarization

PM has also been shown to induce changes in conductance and repolarization of the heart. Duration and morphology of repolarization (the cellular events which occur between heartbeats) may reflect subtle changes in myocardial substrate and vulnerability to PM. There is considerable evidence linking changes in various parameters of cardiac repolarization (e.g., T wave morphology, QT and T wave variability, T wave alternans, and changes in ST segment height) to the risk of sudden death. Humans exposed to ultrafine carbon particles have shown altered repolarization, as indicated by the corrected QT interval on the cardiogram; and this effect persisted to at least 21 hours after exposure (2, 14). Rodent models of susceptibility (monocrotaline-injected or spontaneously hypertensive rats) exposed to ROFA showed exacerbated ST segment depression, a factor which reflects T wave morphology during repolarization and which has been useful in diagnosing patients with ischemic heart disease (15, 16).

Likewise, ambient particles cause exaggerated changes in ST segment elevation in dogs subjected to a controlled occlusion of a coronary artery (12). In contrast to reduced HRV, which may not represent an adverse effect, PM-induced changes in cardiac repolarization are clearly of clinical concern in susceptible populations. Augmenting this concern is recent data from prolonged episodic exposures of otherwise healthy rats to ROFA for 16 weeks (17). Damage to heart tissues of these rats after prolonged exposures would be consistent with conduction abnormalities.

PM Exposure Is Associated with Cardiac Arrythmias and MIs

While PM-induced changes associated with repolarization, conductance, HRV, and HR have the potential to progress to malignant arrhythmias, there is now evidence from both human and animal studies that PM exposure may be linked to severe events directly associated with sudden cardiac death. A recent epidemiological study of patients with implanted cardiac defibrillators reported associations between PM and increased defibrillators discharges, which occur when patients experience significant cardiac arrhythmias (18). Presumably, some of these patients would have suffered a life-threatening event had they not had implanted defibrillators. A second study reported that the risk for MI onset increased in association with PM levels in the 2 hours preceding the MI (19).

PM exposure has been linked with arrhythmia and even death in several toxicological studies. Changes in ECG patterns were reported in dogs exposed to CAPs (12) and rats exposed to urban PM from Ottawa (20). Old rats exposed to New York City CAPs showed a significant increase in the frequency of supraventricular arrhythmias (21, 22). Increased arrhythmia was observed in rats exposed to ROFA or ambient PM; rat models of cardiorespiratory disease showed the most severe changes (23, 15). If an animal model of cardiovascular susceptibility was used, exposure to ROFA resulted in a nearly 50% mortality rate (24, 25).

Taken as a whole, these studies provide convincing evidence that PM exposure can affect critical cardiac events, resulting in altered ECG profiles, arrhythmias, and even death. However, it should also be noted that not all studies have been able to observe these effects (5, 26). Additional work is needed to confirm these findings.

Interaction Between PM and/or Its Soluble Components and the Heart

In addition to affecting the ANS via the lung, it is also possible that PM or its components could directly attack the myocardium. There is substantial evidence that chronic exposure to fibers encountered in the workplace (e.g., asbestos) results in deposition of fibers in organs other than the lung. Some recent ORD studies have suggested that ultrafine PM may exit the lung and deposit in other organs such as the liver and heart (27). So far, these studies have used sources of particles not naturally found in the air (e.g., pure carbon, silver colloid, latex); and not all of the studies are positive (28). Consequently, it is not yet clear to what extent PM actually leaves the lung or whether, if it does leave the lung, to what extent PM interacts directly with the heart.

There is, however, some evidence of direct changes in the myocardium following PM exposure. Rats exposed to ROFA, which is comprised mostly of soluble transition metals, have increased pro-inflammatory cytokine expression in the heart (24). In another study, heart tissue obtained from dogs living in highly polluted Mexico City revealed greater cardiac inflammation and myocyte death compared to hearts obtained from dogs living in areas with low air pollution. In the same study, substantial deposits of PM could be seen throughout the myocardium in the Mexico City dogs (29). *In vitro* studies ongoing at EPA are showing that soluble PM components can directly affect the beating frequency of cardiac cells as well as their ability to communicate with one another. Though preliminary, these observations point to a need for additional work to better define PM-induced effects on myocardial tissue.

PM Exposure Can Affect the Vascular System

Acute coronary events frequently occur as a result of thrombus formation in the site of a ruptured atherosclerotic plaque. Increased levels of clotting and coagulation factors, platelet aggregability, and blood viscosity, together with reduced fibrinolytic activity (ability to dissolve clots) and endothelial cell dysfunction, can promote a pro-coagulant state which could potentially contribute to thrombus formation. C reactive protein, a marker of systemic inflammation which correlates with some cardiac events, has been positively associated with PM in panel studies (30). Some panel studies also report associations between PM and enhanced blood viscosity or increased fibrinogen, a known risk factor for ischemic heart disease (31). Controlled human and animal exposure studies have also reported that exposure to CAPs (in humans) or ROFA (in animals) results in increased levels of blood fibrinogen (32, 33).

Animals exposed to New York CAPs have increased numbers of blood platelets and neutrophils (11). Increased platelets create a more thrombogenic environment, which is even further exacerbated by the presence of pro-inflammatory neutrophils. However, similar changes were not observed with Research Triangle Park CAPs (4). Several ongoing human and animal studies are measuring selected vascular markers of coagulation, clotting, and acute phase response. Preliminary findings thus far do not present a clear pattern. Some studies are reporting PM-induced increases in clotting and coagulation factors and vascular inflammatory cells that suggest PM may alter the coagulation pathways which may trigger cardiovascular events. However, similar studies have not observed these changes. Additional studies will be needed to determine which of these changes, if any, are caused by exposure to ambient PM.

Endothelial cell dysfunction may contribute to myocardial ischemia in some susceptible populations. The vascular endothelium secretes multiple factors that control vascular tone, modulate platelet activity, and influence thrombogenesis. A current EPA study is observing endothelial cell dysfunction in humans exposed to CAPs as measured by dilation of the brachial artery and is confirming an earlier study published by Canadian scientists (34). This vasoconstriction could be caused by an increase in circulating endothelin-1, a protein that has been reported to be increased in rats exposed to PM (35). *In vitro* studies using endothelial cells show that metals associated with PM emissions activate several genes that alter cell function, activating them to produce inflammogenic mediators that may represent an early part of a clotting event.

Collectively, it appears that PM can affect the vascular system by creating a more thrombogenic environment. However, additional studies are needed to determine the exact pathways and mechanisms by which these changes are caused.

Programmatic Need and Relevance

There are several complex pathways by which PM may be exerting its effects. Because PM is a complex mixture exhibiting many different chemical and physical properties, it is likely that more than one pathway is activated depending on the individual properties of specific PM samples and perhaps on the health status or genetic make-up of the host. Results reported from panel studies, controlled human exposure studies, and animal toxicological studies, though small in number, are generally coherent with the epidemiological findings of associations between PM and increased mortality or hospital admissions for CVD. Furthermore, they add support to specific hypotheses regarding the possible mechanisms by which PM exposure may be linked with adverse cardiac outcomes. Defining a credible mechanism or mode of action will enhance the assessment of risk both qualitatively and quantitatively. Because cardiac events represent the number one killer of U.S. adults, findings that link PM and cardiac events are of tremendous importance.

Future Directions

Five years ago, a description of PM health effects would typically include a caveat that the underlying biological mechanisms were largely unknown. As summarized previously, the scientific literature is now rapidly expanding with hypotheses concerning plausible mechanistic pathways by which PM could cause adverse effects. However, research is still far from clearly explaining the pathways by which very small concentrations of inhaled ambient PM can produce the cardiovascular and pulmonary changes that can contribute to increased mortality/morbidity. Therefore, research on the adverse cardiovascular effects of PM needs to be expanded, particularly among individuals with CVD. Based on existing epidemiological and experimental data, 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. ORD, through its intramural and extramural programs, will be focusing specifically on these early and primary events to separate the effects of PM among other stressors. The roles of pre-existing disease and other features bearing on susceptibility are likely to be key to the health observations.

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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

The statistical association between ambient concentrations of PM and health outcomes (mortality and morbidity) provides evidence that exposure to ambient PM may have an adverse effect on human health. However, sophisticated statistical techniques are required to identify the effects of PM in the presence of many other causes of mortality and morbidity. Thus, concerns have arisen over the reliability of the statistical models and possible effects of measurement error or misclassification on estimates of health risks.

Key Uncertainties

Current epidemiological research finds that per 10 $\mu g/m^3$ increase in ambient PM concentrations, there are excess risks of mortality of a few tenths of a percent to a few percent in the general population. Obtaining statistical significance on this scale places stringent demands on statistical analysis techniques. Sophisticated models are required to control for mortality associated with season, temperature, epidemics, etc. Understandably, concerns exist regarding a variety of statistical and exposure classification issues.

Major Accomplishments

Statistical Methods

In 1998, EPA and the National Research Center for Statistics and the Environment at the University of Washington organized a Workshop on Particulate Methodology to explore issues related to analysis and measurement. As discussed in following text, significant progress has been made in addressing many of the statistical issues emphasized in the workshop report (1).

Multi-city Analyses

Time-series analyses were initially conducted on a single location selected primarily on the basis of data availability. New techniques have been proposed for combining results from several studies; and studies of more formal, multi-city designs have been conducted. NMMAPS was a pioneering effort that used a sampling frame defined by U.S. counties (2). The 90 largest urban areas (by population) were selected, and the daily mortality data for 1987–1994 were analyzed using a common statistical protocol to evaluate associations with PM and other pollutants. In the multi-city approach, the potential selection bias of only a single or a few locations is avoided. Additionally, publication bias from reporting only positive results is avoided because results are reported for all cities selected for the multi-city study.

Spatial Analytical Methods

In the analysis of data from studies that examine the association between city-specific mortality and long-term average pollutant concentrations, an important issue is whether observations of individual subjects are independent or correlated. Spatial correlation in mortality can result from social and physical environments of residents of the same city. Air pollution can be spatially autocorrelated as a result of broad regional patterns stemming from source and dispersion patterns. In a recent re-analysis of data from a study that examined associations between mortality and fine-particle and sulfate concentrations in 154 cities throughout the U.S., new methods were developed and applied to allow for the presence of spatial autocorrelation in the data (2).

"Harvesting"

"Harvesting", in the context of time-series mortality studies, refers to the question of whether deaths from air pollution occur in people who are highly susceptible and near death (and who 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. Many studies have identified associations between daily mortality and air quality variables measured at the time of or a few days before deaths, but until recently it has not been possible to fully address the issue of "harvesting". A newly developed methodology−the constrained, distributed lag model−makes it feasible to better understand the time course of deaths related to air pollution exposures (3). Recent studies using this technique suggest that, at most, only a small fraction of the deaths associated with air pollution in daily time-series studies can be attributed to short term mortality displacement (4, 5). Several other analytical approaches have also been proposed to address "harvesting" (6). The various approaches have been applied to several locations and provide little evidence for "harvesting". However, these approaches need to be tested on additional data sets and refined to better quantify the degree of life-shortening associated with PM and other pollutants.

Dose-Response/Threshold Issues

There has been considerable controversy over the question of whether there is a threshold value below which PM exposure is not harmful and whether the dose-response (or exposure-response) relationship is linear. To date, studies of PM health effects suggest a no-threshold, linear dose-response relationship. If there are thresholds for the effects of PM on deaths or hospital admissions, health effects may be overstated. A new methodology has been developed that allows smoothed dose-response curves from multiple locations to be combined, and its effectiveness has been demonstrated using simulation studies (4). Analysis of daily deaths in 10 U.S. cities showed no deviation from linearity down to the lowest exposure concentrations (7) when statistical methodologies to incorporate heterogeneity across cities were used (8).

Confounding

In attempting to set policy based on epidemiological results, there is always the concern that another, unmeasured indicator highly correlated with the measured indicator is responsible for all or some of the observed relationship. In PM epidemiology, gaseous co-pollutants (CO, NO_2, SO_2, O_3) are considered potential confounders. This possibility has frequently been investigated by including a PM indicator and one or more gaseous co-pollutants in a multiple pollutant model. Progress has been made in understanding how one pollutant can yield an association with health effects, even though the health effects are caused by a second pollutant (9). The dependence of this effect on the correlation coefficient between the pollutants, the relative toxicity, and the error in each indicator has been investigated (10). A hierarchical model to assess the confounding effect of gaseous co-pollutants for both morbidity and mortality in multi-city studies has been developed and applied to examine the association between PM_{10} and daily deaths (2). The results of this analysis suggest that associations were not confounded by gaseous air pollutants.

Model Specification

While there has been general agreement among epidemiologists and biostatisticians on how to formulate models for time-series analyses, there are many possibilities for smoothing functions to account for the relationships of health effects with temperature, humidity, and season. Several studies have investigated the sensitivity of estimated health risks to variations in smoothing function, including Bayesian approaches which compare thousands of possible models (11). Other studies have investigated the possible confounding effects of epidemics and the relationship of temperature and humidity with mortality to guide selection of lags and functions for use in smoothing (12–14).

Statistical Techniques

The application of the time series has been facilitated by recent advances in computer hardware and by the development of statistical software that appropriately accounts for the data structure of the daily time series. Nonparametric smoothing techniques have facilitated accounting for health outcomes associated with temperature, humidity, and season. However, epidemiologists and biostatisticians have recently recognized two problems. When nonparametric smoothing is used in GAMs, the default iteration criteria are not adequate to ensure convergence. In addition, an approximation used to estimate the standard error yields values that are too low. As a result, the default GAM technique frequently predicted too high an estimate of risk and too low a standard error.

To address this issue, ORD invited authors of papers relevant to the PM standard-setting process to re-analyze their data using more stringent GAM convergence criteria and also using only parametric smoothing functions which permit exact calculation of standard error. The workshop was held November 4–6, 2002, and led to a substantial clarification of the potential effects of problems in the use of GAM. Two new statistical techniques were presented which avoid the problems with GAM. The workshop also featured a discussion of model selection and sensitivity analysis. The results of the re-analyses were peer-reviewed by an HEI committee and was recently published as an HEI report (15). The existence of a statistical link between exposure to ambient PM and health outcomes remains valid.

Alternative Statistical Techniques

The Poisson log-link approach to time-series analysis is popular and has proven useful. However, a number of alternative approaches have been developed. A very promising approach is the case-crossover technique, which, by design, avoids some of the smoothing problems encountered in the Poisson approach but appears to give comparable health risks for PM (16, 17). A number of methodological papers have examined the potential for bias and confounding in this approach and developed new statistical methods to overcome these problems (18–20). Another alternative approach applies additive mixed models to the relationship between air pollution and health (21). The mixed model approach does not have the shortcomings of the GAM because it provides accurate standard errors and does not use back-fitting. This approach can provide smoothed dose response curves against multiple predictors for Poisson data. It is currently being applied to the re-examination of the association between PM_{10} and hospital admissions.

Measurement Error and Misclassification

Measurement error and misclassification refer to a variety of errors arising from the use of ambient concentrations measurements as an indicator of exposure.

Spatial Error

An error or bias may be introduced into the estimated health risk if the measured ambient concentration value, either from one site or the average of values from several sites, is not representative of the community-wide average. The spatial correlation between PM_{10}, gaseous pollutants, and weather parameters has been investigated in the north-central U.S. (22). In ongoing work, $PM_{2.5}$ and $PM_{10-2.5}$ values from the National Monitoring Network are being used to investigate the spatial variability of $PM_{2.5}$ and $PM_{10-2.5}$ in cities across the U.S. In other studies, the spatial variability of chemical components and source category contributions are being examined. $PM_{2.5}$ and sulfate appear to be reasonably uniform in many cities. However, $PM_{10-2.5}$, other chemical species, and some source categories may not be so uniformly distributed.

Difference Between Ambient Concentration and Exposure

Total personal exposure is composed of two major components: ambient exposure (due to exposure to ambient PM while outdoors and to ambient PM which has infiltrated indoors while indoors) and non-ambient exposure (due to exposure to PM from indoor and personal sources). Ambient exposure is attenuated relative to ambient concentration (i.e., the concentration of ambient PM indoors is less than ambient PM outdoors). For epidemiological studies using ambient concentrations as an exposure indicator, ambient exposure is usually the exposure of interest. However, in some situations, the non-ambient exposure may be important or the association of non-ambient exposure with health outcomes may be studied. The ambient concentration and the total personal exposure may be measured, but ambient and non-ambient exposure must be estimated using other information.

As discussed under Research Topics 1 and 2, EPA has an extensive program devoted to studying the relationships between ambient concentration, total personal exposure, ambient exposure, and non-ambient exposure. Work in progress suggests that, as long as non-ambient exposure is independent of ambient concentration, values of the health risk associated with ambient concentration (C) and values of the health risk associated with ambient exposure (A) will not be changed by inclusion of health effects due to non-ambient exposure in the health-outcome time series. However, C will be biased low compared to A by the ratio ambient exposure/ambient concentration; i.e., C = ambient exposure/ambient concentration or A/C. A/C will give the reduction in health risk that would be expected from a reduction in ambient concentration. Therefore, it is a parameter of interest to local public health officials. However, C will differ from city to city because of differences in building characteristics and time spent outdoors.

Uncertainties in the Measurement of Ambient Concentrations

Precision

The FRMs for PM, as discussed in "Research Topic 11," provide a precise measurement of the mass of PM remaining on a filter after equilibration. However, because there is no standard measurement method for suspended PM, it is not possible to measure accuracy except in terms of the precision with which a candidate sampler agrees with a reference sampler.

Loss of Semivolatile PM Mass in PM Measurements

Semivolatile PM includes ammonium nitrate and semivolatile organic compounds (SVOCs) that exist in the particulate phase in the atmosphere but evaporate from filters during sampling and storage. EPA has supported the development of monitors with the potential for batch and continuous measurements of both the semivolatile and nonvolatile components of PM (23). These monitors, other continuous monitors, and the FRM have been intercompared for a 2-year period in Salt Lake City, UT, and for episodic periods in other cities (24). These studies have provided new information on the amount of semivolatile components lost by the FRM and by other continuous monitors at various sites in the U.S. and on the seasonal variations and sources of semivolatile PM (25). This program also led to the development of a technique for artifact-free measurement of nonvolatile and semivolatile OC that could be used in the EPA speciation network. Currently, measurement of OC mass is influenced by positive artifacts (due to absorption of organic vapor by the quartz filter) and by negative artifacts (due to the evaporation of semivolatile OC).

Alternate Indicators

EPA is conducting additional studies to develop monitors for other parameters and to use alternate indicators in epidemiological studies. Among these efforts is EPA's support of the Rochester PM Research Center, which emphasizes health effects associated with exposure to ultrafine particles. However, there are currently no convenient ways to measure an indicator of ultrafine particles. EPA has supported the development of a monitor, the electrical aerosol detector, that may serve as an indicator of the amount of ultrafine PM deposited in the lung (26). In addition, the long-term monitoring studies supported by EPA in Phoenix provide adequate information for conducting epidemiological studies with several alternate indicators, including $PM_{1.0}$ and $PM_{2.5}$ measured by tapered element oscillating microbalance (TEOM) and filters (27).

Source Category Contributions

EPA scientists are currently using time series of source category contributions from EPA studies in Phoenix, AZ, and Philadelphia, PA, as exposure indicators in epidemiological analyses.

Programmatic Need and Relevance

Epidemiological studies have played a critical role in previous PM NAAQS reviews and will likely do so in the future. Quantitative assessments of risk and health benefits assessments have relied upon the concentration-response functions from epidemiological studies. Further exploration of methodological issues in the epidemiological analyses is expected to result in better assessment of these functions and reduce uncertainty in findings.

Future Directions

New techniques for statistical analysis and model selection presented at the November 2002 EPA GAM workshop will be used in further epidemiological analyses and should lead to better scientific understanding and public acceptance of epidemiological results. EPA scientists participated in the PM Research Center workshop to compare source category estimates derived from different receptor models using a common data set and to use a time series of source category contributions as alternate indicators of exposure. In this regard, measurements of speciated PM at national PM monitoring sites in several cities will provide the basis for epidemiological studies capable of providing information concerning the time structure of health responses to PM exposure.

New techniques for measuring ultrafine PM and semivolatile as well as nonvolatile PM mass will be improved and can add to the existing data for epidemiological studies. Epidemiological studies in individual cities with low spatial variation of PM concentration and that cover a range of climatic conditions (temperature, relative humidity, seasonality) will be very useful in sorting out the relative effects of pollution and weather factors. Exposure studies, in conjunction with measurements of health outcomes, will permit investigation of associations of health effects with ambient and non-ambient exposure as well as with ambient concentration and total personal exposure. Statistical simulations will be used to quantitatively investigate the effect of spatial variability on health risk estimates. The addition of city-specific data for key model inputs (i.e., housing characteristics and human activity patterns) will permit analysis of city-to-city variability in the ratio of ambient exposure to ambient concentration and in the amount of non-ambient exposure.

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Technical Support

What are the concentrations of PM and PM components in the ambient atmosphere and how do they vary over time and space?

Introduction

Atmospheric PM, comprising solid and liquid particles suspended in air, has both natural (earthen or biogenic) and anthropogenic sources. Ambient PM is either emitted directly into the air as primary particles or is formed through chemical reactions among mixed gas phase materials and sunlight while drifting through the atmosphere. The resulting distribution of ambient PM includes particles that may span five to six orders of magnitude in size and exhibit a wide diversity of chemical and physical properties. The major chemical components of fine PM ($PM_{2.5}$) are sulfate, nitrate, ammonium, carbonaceous material (OC, composed itself of hundreds of organic compounds, and EC or black carbont). Coarse PM ($PM_{10\text{-}2.5}$) is composed of primarily crustal material (typically oxides or salts of elements found in dirt; e.g., Fe, Ca, Si, Al).

Measurement of atmospheric PM is fundamental for evaluating and managing air quality. It serves multiple purposes, from providing key inputs to health effects research to understanding atmospheric processes and chemistry, relating PM observed at a monitoring site to its sources, and supporting NAAQS implementation. EPA's research to support atmospheric PM measurement can be broken down into five areas:

(1) Federal Reference Method (FRM) Program
- Produces reference methods as metric of air pollution related to health effects
- Revises and improves reference methods
- Evaluates alternatives for equivalency to reference methods

(2) Measurement of PM species
- Develops, improves, evaluates, and inter-compares methods to measure PM species
- Provides basic PM species and source information

(3) Field Studies
- Provides national leadership and coordination for broad scale field measurement campaigns

(4) Advanced Measurement Techniques
- Maintains state of the art measurement capability for measuring particles

(5) Network Design and Implementation
- Provides a major supportive role to OAR in monitoring strategy development and implementation, including network evolution and application of new technology

By virtue of its complex nature, no single measurement method can both collect and analyze PM; thus, measurement of atmospheric PM is accomplished via a number of measurement and analysis methods. Historically, PM has been collected on filters with subsequent chemical analysis in the laboratory. Many of these PM collection methods are less than optimal because they are time-consuming, provide limited temporal data, and are prone to interferences or biases that create uncertainty in the measurement. Because they are also expensive, spatial coverage of sampling is generally restricted. Recent developments in continuous and semi-continuous methods provide considerable improvements in temporal resolution of PM concentrations (1–3). Single particle mass spectrometers, also recently developed, provide continuous composition by size. At present, however, these methods are mostly qualitative; detailed quantification requires additional co-located measurements of PM by size using integrated filter measurements or impactors. EPA is cooperating with many other organizations, both public and private, to perform research to improve collection and analysis methods that produce the measured values observed in PM monitoring networks, such as EPA's National Monitoring Network.

Key Uncertainties, Objectives, and Special Issues

The FRMs for $PM_{2.5}$ and PM_{10} are based on collecting PM on filters over 24-hr sampling periods to measure PM mass in ambient air (40 CFR Parts 50-53, 58). However, gas-solid phase partitioning, which is affected by a number of environmental variables, as well as the collection process itself, results in significant uncertainty in the measurement of PM mass, even by the FRMs. In addition, sample handling, storage, and equilibration of filters introduce errors into the measurement. Filter collection also limits most speciated sampling to a 1-in-3 or 1-in-6 day sampling schedule, thus greatly limiting temporal evaluations of the nature of PM concentrations, which have been shown to have considerable diurnal variation.

The collection and analysis of PM components is fraught with problems due to the complex nature of aerosols. While some compounds like ammonium sulfate are stable (nonvolatile), others such as ammonium nitrate and a large fraction of the organic material exist in both the gas and aerosol phase under normal ambient conditions. Collection of these species is difficult, and biases arise when PM is collected using traditional filter-based methods. Improved methods have been developed for nitrate, but the collection of OC remains problematic (4–6). Measurements of OC is particularly difficult because it is composed of hundreds or even thousands of species of which only about 15–20% have been identified and quantified.

The semivolatile nature of many of the organic compounds also makes collection difficult (4, 7). Aside from difficulties associated with the collection of PM, the analytical methods are problematic, especially for carbonaceous material, which can be divided into two categories: OC and EC.

Separating carbonaceous material into OC and EC is often done as a first cut at better understanding PM composition. Methods for measuring OC and EC exist and have been widely used, but the methods differ substantially in their results, especially for EC. In fact, recent comparisons of the two methods being used in EPA's National Monitoring Network, IMPROVE and the $PM_{2.5}$ STN, indicate a difference by a factor of two in EC values (8). Efforts are underway to better understand the relationships between measurements taken using these two methods.

Advances have been made in PM measurement techniques, but much remains to be done to bring newer techniques into wider application. Continuous and semi-continuous methods for PM mass (fine, coarse, and PM_{10}) and its major components of PM are emerging. While some of these methods are commercially available, the uncertainties in their measured values are still unknown and greatly limit their use. Advanced methods for measuring the chemical composition and physical properties of single particles also are emerging (9). However, many of the single-particle methods are qualitative; and, like many advanced techniques, their operation is subject to problems and requires highly trained personnel.

Finally, a major shortcoming in our understanding of the uncertainties associated with PM measurements is the lack of appropriate reference standards and standard reference materials. While precision can be obtained for the overall measurements (collection and analysis) by co-locating multiple samplers, the accuracy of these measurements is unknown (5). To date, the best approach to evaluation has been looking at equivalency to other methods.

Major Accomplishments

Several major accomplishments in the technology used to measure PM have been achieved over the last five years, many in coordination with OAR and the greater scientific community. These are summarized in following text using the five broad areas of the EPA atmospheric PM measurement research outlined in the introduction to this section.

FRM Program

EPA developed and evaluated the FRM for $PM_{2.5}$ (10). This method is being used in the National Monitoring Network to measure $PM_{2.5}$ mass concentrations for comparison to the $PM_{2.5}$ NAAQS levels. With the potential for a PM coarse particle standard and in cooperation with the Los Angeles Supersites project (refer to the following Field Studies section), EPA has developed a continuous coarse particle sampler (11). This sampler will be evaluated by EPA as a possible FRM or equivalent. EPA has also evaluated numerous methods submitted by organizations outside EPA for reference and equivalency to the FRM. Since 1997, ORD has evaluated and approved 10 applications for PM_{10} reference method designations, 10 applications for $PM_{2.5}$ reference method designations, and four applications for $PM_{2.5}$ equivalent method designations.

Measurement of PM Species

EPA has established the $PM_{2.5}$ STN and was the first to evaluate the newly developed chemical speciation samplers prior to their implementation in the National Monitoring Network (12, 13). Results suggested areas for modifications to the samplers, and many of these were implemented and confirmed in a second intercomparison study in conjunction with the first of EPA's PM Supersites projects in Atlanta, GA (2) (refer to the following Field Studies section). The IMPROVE and STN analysis methods for determining concentrations of OC and EC on quartz fiber filters have been compared, and the results of this study have led to the current STN analysis protocol (8). EPA has performed and continues to perform research to improve the understanding of the differences between these two national networks.

EPA, in conjunction with the National Institute of Standards and Technology (NIST), has established the $PM_{2.5}$ Organic Working Group to conduct inter-laboratory trials that will allow the comparison of measurements for various organic species among the participants (PM Supersites, PM research centers, and other investigators); the establishment of consensus reference values for organic species in PM standard reference materials; and the development of calibration and reference standards for the analysis of organic compounds in atmospheric PM with an emphasis on important source apportionment tracers for sources potentially related to adverse health effects (14). The project is in Phase II with about 20 laboratories participating nationwide.

Researchers funded by ORD through the STAR Program significantly contributed to the ability to measure PM species, as well as to evaluate the FRM. Progress involved either continuous and semi-continuous monitor development (e.g. 15–18) or the evaluation and improvement of collection techniques (e.g. 19–25).

Field Studies

EPA established a regionally based ambient monitoring program known as the PM Supersites Program to provide critical information and data to better understand atmospheric processes and source-receptor relationships and to support health effects and exposure research. The program has also provided a mechanism to test and compare advanced measurement methods. Phase I of the Supersites Program included studies in Atlanta, GA, and Fresno, CA. Phase II includes studies in New York, NY; Baltimore, MD; Pittsburgh, PA; St. Louis, MO; Houston, TX; and Fresno and Los Angeles, Ca. Initiated by ORD and the head of the CASAC Fine Particles Subcommittee, the five eastern PM Supersites projects were organized into a uniform intensive sampling program (July 2001–January 2002) with over 20 other studies coordinated to form what has become known as the Eastern Supersites Program (ESP).

The database from these intensives is being compiled and will include all aerometric data collected in the U.S. for a 13-month period beginning June 28, 2001. This will be the largest air quality database ever established and will be used by EPA and others to evaluate national and regional air quality models. The data gathering phase of PM Supersites Program will end in 2004 when data from each Supersite project will be submitted to two databases: the NARSTO Permanent Data Archive and the Supersite Integrated Relational Database. The data analysis phase was initiated in 2003 and will continue through 2005.

EPA has also participated in studies conducted by the SOS in the southeastern U.S., specifically in Atlanta, Nashville, and Houston. Novel methods were used for sample collection, followed by advanced extraction and analysis techniques to determine concentrations of organic aerosols and SVOCs. EPA personnel conducted the measurements at these locations. In addition to the SOS studies, a major STAR Program grant supported field measurements in Philadelphia during 1998, 1999, and 2000 through the Northeast Oxidant and Particle Study (NE-OPS) campaign.

Advanced Measurement Techniques

EPA established a state-of-the-art organic analysis laboratory, scanning electron microscope (SEM) laboratory, and trace elements x-ray fluorescence (XRF) laboratory. These laboratories are used for methods development and evaluation, and they support other programs by providing advanced chemical analyses. The SEM laboratory has developed state-of-the-art methods for the chemical and morphological analysis of single particles on filters. These results have been used in studies to apportion the measured PM observed at a receptor site back to its sources (26–28).

A number of advanced measurement methods were compared during the Atlanta Supersites Project (1–3, 9, 29). Results indicate reasonable agreement among methods measuring the same parameter for most species with highly trained personnel operating many of these instruments. The Atlanta Supersites Project has resulted in nearly 25 publications; 15 of which are included in a special issue of the Journal of Geophysical Research – Atmospheres (2).

The STAR Program-funded Southern Center for the Integrated Study of Secondary Air Pollutants (SCISSAP) developed and field-tested several instruments: (a) Particle Composition Monitor (PCM) and related laboratory analytical techniques for measuring the mass and composition of $PM_{2.5}$ as well as its precursor compounds using the filter-denuder technique; (b) Differential Mobility Analyzer-Aerosol Particle Mass Analyzer (DMA-APM) for in situ measurements of particle mass as a function of mobility (i.e., size); and (c) a system for quantifying in situ concentrations of oxygenated VOCs. The key SCISSAP findings point toward a regionally distributed source of fine particles and indicate that over 60% of the $PM_{2.5}$ mass is comprised of sulfate and organic compounds. The DMA-APS

instrument provides a precise and accurate technique for measuring particle density. Observations in Atlanta show two distinct types of particles: the "low density" particles have densities similar to DEPs, and the "high density" particles are consistent with particles consisting primarily of OC and sulfates (30). Investigators participated in several field studies, including the 1999 SOS Nashville/Middle Tennessee Ozone Study, the 2000 Texas Air Quality Study, and the Atlanta Supersite Program (31, 32).

Through STAR Program grants, ORD has invested in the development of real-time single particle measurement techniques. Advances include development of the aerosol mass spectrometer that can quantify in real time the amount of size- and composition-resolved PAHs (33); development of an instrument capable of distinguishing $PM_{2.5}$ constituents such as OC, EC, and inorganic compounds in the ultrafine sizes (34); improvement of methods to speciate volatile and reacting compounds in single particles by on-line laser desorption ionization mass spectrometry (35, 36); development of real-time chemical analysis of organic aerosols using a thermal desorption particle beam mass spectrometer (37); and improvement of methods to quantify single-particle field measurements (38–40).

Network Design and Implementation

ORD's atmospheric measurements research has made substantial contributions to the development of the new "National Ambient Air Monitoring Strategy" recently released by the Office of Air Quality, Planning, and Standards (OAQPS) for external review (41).

Programmatic Need and Relevance

Measurement methods including collection and analysis methods are critical to understanding the accumulation of PM in air, linking pollutants at monitoring sites back to their sources, developing control strategies for minimizing pollution levels, and understanding health and welfare effects of PM and other pollutants. No method will perfectly measure the concentration of PM in air, so there is a critical need to determine the accuracy with which methods estimate concentrations. Much of the work conducted by EPA is designed to develop methods and evaluate their uncertainty, a task which is hampered by the lack of reference standards. At best, precision and equivalency is obtained by comparison to other methods that also are prone to undefined uncertainties. $PM_{2.5}$ and PM_{10} mass are currently the indicators for NAAQS. Consequently, defining the uncertainty associated with these measures is critical because areas that exceed the standards will be required to develop plans for reducing pollution levels in the affected areas. The promulgation of a coarse particle standard (i.e., particles measuring between 10 and 2.5 microns) is expected within the next 2 years, and the uncertainty with these methods will also need to be established. Future research will continue to define and minimize uncertainty in the measurements by developing standards and by improving methods for collection and analysis of PM.

Future Directions

OC and EC, organic aerosols species, and SVOCs make up 20–70% of the mass of $PM_{2.5}$ nearly everywhere in the country at all times. However, to date, EPA has been unable to collect the organic fraction of the aerosol without significant bias (positive and negative); and the uncertainties associated with its measurement, including collection and analysis, are often undefined or very large. For example, of the four chemical speciation monitors evaluated for the National Monitoring Network, the measurement of OC had an estimated uncertainty of more than 30% based on a comparison of the methods used. For EC, the uncertainty estimate rose to 200% depending on the analysis method. This uncertainty is still just a measure of comparability of very similar methods while the uncertainty associated with how well we determined what was actually in the air is undefined and may be off by a significant amount. The uncertainties for measuring mass, sulfate, nitrate, and trace metals range from 10–20%, but the accuracy relative to a reference standard is still unknown, as is how well the reported data represent what is actually present in air.

While the development and improvement of methods to measure speciated PM are of utmost importance to EPA's National Monitoring Network program, this program will also require continued support for measuring PM mass. As mentioned previously, a coarse PM NAAQS is expected to be promulgated in the next 2 years and will need an FRM. Additionally, the states, which carry out the monitoring of PM, are extremely interested in replacing labor-intensive, filter-based monitoring methods with continuous methods.

Given these issues, future EPA efforts will continue to emphasize improving collection and analysis methods for OC and EC; continuing to develop, improve, and evaluate continuous methods for all major components of PM; and developing and evaluating methods for the measurement of coarse particles. Many of these evaluations will occur in conjunction with EPA's PM Supersites Program and throughout ORD to help ensure compatible measurements with emissions estimates and health and exposure studies. EPA will continue to provide direction to the states and local and tribal communities and will continue to support the National Monitoring Network to ensure that these networks obtain data that are defensible and of known uncertainty. EPA will continue to coordinate with other federal agencies, either directly or through various air quality subcommittees, such as CENR, NARSTO, and others, as well as the private sector. EPA's role in future years will be to lead PM methods research both in direction and products.

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Appendix C

CENR Air Quality Research Subcommittee Particulate Matter Workgroup

This appendix lists members of the CENR Air Quality Research Subcommittee Particulate Matter Workgroup, a federal coalition of agencies and departments with vested research efforts and interest in air quality as it relates to PM.

Department of Agriculture

- Agricultural Research Service
- Cooperative State Research, Education, and Extension Service
- Forest Service
- Natural Resources Conservation Service

Department of Commerce

- National Institute of Standards and Technology
- National Oceanic and Atmospheric Administration

Department of Defense

Department of Energy

Department of Health and Human Services

- Centers for Disease Control and Prevention
- National Institutes of Health

Department of Housing and Urban Development

Department of the Interior

- Geological Survey
- National Park Service

Department of State

Department of Transportation

- Federal Aviation Administration
- Federal Highway Administration

Environmental Protection Agency

National Aeronautics and Space Administration

National Science Foundation

Office of Management and Budget

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