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HEI's National Particle Component Toxicity (NPACT) Initiative

HEI NPACT Review Panel

EXECUTIVE SUMMARY

Health Effects Institute

ABOUT HEI

The Health Effects Institute is a nonprofit corporation chartered in 1980 as an independent research organization to provide high-quality, impartial, and relevant science on the effects of air pollution on health. To accomplish its mission, the institute

- Identifies the highest-priority areas for health effects research;
- Competitively funds and oversees research projects;
- Provides intensive independent review of HEI-supported studies and related research;
- Integrates HEI's research results with those of other institutions into broader evaluations; and
- Communicates the results of HEI's research and analyses to public and private decision makers.

HEI typically receives half of its core funds from the U.S. Environmental Protection Agency and half from the worldwide motor vehicle industry. Frequently, other public and private organizations in the United States and around the world also support major projects or research programs. For the research funded under the National Particle Component Toxicity initiative, HEI received additional funds from the American Forest & Paper Association, American Iron and Steel Institute, American Petroleum Institute, ExxonMobil, and Public Service Electric and Gas.

HEI has funded more than 280 research projects in North America, Europe, Asia, and Latin America, the results of which have informed decisions regarding carbon monoxide, air toxics, nitrogen oxides, diesel exhaust, ozone, particulate matter, and other pollutants. These results have appeared in the peer-reviewed literature and in more than 200 comprehensive reports published by HEI.

HEI's independent Board of Directors consists of leaders in science and policy who are committed to fostering the public–private partnership that is central to the organization. The Health Research Committee solicits input from HEI sponsors and other stakeholders and works with scientific staff to develop a Five-Year Strategic Plan, select research projects for funding, and oversee their conduct. The Health Review Committee, which has no role in selecting or overseeing studies, works with staff to evaluate and interpret the results of funded studies and related research. For the NPACT studies, a special NPACT Review Panel — comprising Review Committee members and outside experts — fulfilled that role.

All project results and accompanying comments by the Health Review Committee are widely disseminated through HEI's Web site (*www.healtheffects.org*), printed reports, newsletters and other publications, annual conferences, and presentations to legislative bodies and public agencies.

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INTRODUCTION

Findings from epidemiologic and controlled-exposure studies about the health effects of particulate matter (PM*) have led the U.S. Environmental Protection Agency (U.S. EPA) and other regulatory agencies to establish mass-based ambient air quality standards for PM within a specific size range. PM with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$) is considered to be particularly important because the small particles can be easily inhaled. Because the composition of PM is complex, there has long been a question as to whether some components of the PM mixture are of greater public health concern than others. Obtaining this information would help focus efforts to reduce people's exposure by enabling the control of those sources that contribute most of the toxic components in the PM mixture.

Detailed information on $PM_{2.5}$ composition began to be collected systematically in the year 1999, in what was then called the Speciation Trends Network (currently the Chemical Speciation Network [CSN]). In an effort to consolidate the available data from several data sources and make them more accessible to researchers, HEI funded the company Atmospheric and Environmental Research through a December 2003 Request for Proposals (titled *To Create a Database of Air Pollutant Components*) to set up and maintain such a database. The resulting HEI Air Quality Database (*https://hei.aer.com*) was launched by Atmospheric and Environmental Research in September 2005 and comprises data from the U.S. EPA's monitoring

This Executive Summary is excerpted from Research Report 177, by Morton Lippmann and colleagues, and Research Report 178, by Sverre Vedal and colleagues. Each of these reports contains a Commentary and a Synthesis by the HEI NPACT Review Panel. Full citations for the reports can be found on the back cover of this document.

Although this document was produced with partial funding by the United States Environmental Protection Agency under Assistance Award CR–83234701 to the Health Effects Institute, it has not been subjected to the Agency's peer and administrative review and therefore may not necessarily reflect the views of the Agency, and no official endorsement by it should be inferred. For the research funded under the National Particle Component Toxicity initiative, HEI received additional funds from the American Forest & Paper Association, American Iron and Steel Institute, American Petroleum Institute, ExxonMobil, and Public Service Electric and Gas. The contents of this document also have not been reviewed by private party institutions, including those that support the Health Effects Institute and this research initiative; therefore, it may not reflect the views or policies of these parties, and no endorsement by them should be inferred.

* A list of abbreviations and other terms appears at the end of the Executive Summary.

What The NPACT Initiative Adds

- In this comprehensive and ambitious program, Lippmann and Vedal and their respective colleagues performed coordinated nationwide epidemiologic and toxicologic studies of the health effects of PM and its components. These studies mark an important addition to air quality and health research.
- Lippmann and colleagues conducted studies in mice and in human cell lines exposed to ambient PM and epidemiologic studies of short- and long-term cardiovascular effects. Their study has provided new insights into the toxicity of components and source categories, and identified the Coal Combustion, Residual Oil Combustion, Traffic, and Metals source categories as most consistently associated with health effects. However, other components and source categories could not be definitively excluded as having no adverse effects.
- Vedal and colleagues' study of the cardiovascular effects of PM components focused on traffic sources. They evaluated data from the Multi-Ethnic Study of Atherosclerosis and Women's Health Initiative–Observational Study cohorts and exposed mice to combinations of mixed vehicular engine emissions and non-vehicular PM. They found strong evidence for associations of $PM_{2.5}$, organic carbon, and sulfur with subclinical and clinical outcomes in the cohorts, with less evidence for elemental carbon. Their toxicologic study provided strong evidence for effects of mixed vehicular engine emissions and, to a lesser extent, exhaust gases on vascular markers in mice. Non-vehicular PM induced few effects.
- Taken together, the NPACT studies, which are to date the most systematic effort to combine epidemiologic and toxicologic analyses of these questions, found associations of secondary sulfate and, to a somewhat lesser extent, traffic sources with health effects. The HEI NPACT Review Panel concluded, however, that the studies do not provide compelling evidence that any specific source, component, or size class of PM may be excluded as a possible contributor to PM toxicity.
- Better understanding of exposure and health effects is needed before it can be concluded that regulations targeting specific sources or components of $PM_{2.5}$ will protect public health more effectively than continuing to follow the current practice of targeting $PM_{2.5}$ mass as a whole.

networks, particularly concentrations of $PM_{2.5}$ components and gaseous pollutants at and near sites in the CSN and state, local, and tribal air monitoring stations. Currently, the database contains information on speciated PM components and gaseous pollutants at these sites for the years 2000 to the present.

While the Air Quality Database was under construction, HEI issued Request for Applications (RFA) 05-1-A, *Conducting Full Studies to Compare Characteristics of PM Associated with Health Effects*. Its goal was to support integrated multidisciplinary studies — including epidemiology, toxicology, exposure science, and statistics — to investigate the health effects of PM components in humans and animal models at locations across the United States where PM sources and components differ. The comparison of PM component effects was to be made in the context of the contribution of gaseous copollutants to the air pollution mixture and its health effects, as well as to PM-related toxicity and health effects.

RFA 05-1-A was accompanied by RFA 05-1-B, *Conducting Planning or Demonstration Studies to Design a Major Study to Compare Characteristics of PM Associated with Health Effects*, in order to provide a smaller amount of funding to multidisciplinary study teams that had not previously worked together. These teams would then conduct planning or demonstration studies to gather and analyze the data necessary to design a full study of the toxicity of PM components, similar to those funded under RFA 05-1-A.

DESCRIPTION OF THE NATIONAL PARTICLE COMPONENT TOXICITY INITIATIVE

HEI's National Particle Component Toxicity (NPACT) initiative was launched in view of emerging evidence that the composition of PM is different in different places as well as that there are geographic differences in the toxicity of PM across the country. Given the complexity and importance of these issues, HEI organized several workshops and held extensive discussions and consultations about the best approaches to investigate these questions. These deliberations resulted in the publication of several RFAs and the funding of two major studies. The primary goal of the NPACT initiative was to determine if components of PM from various sources are equally toxic to health, or if some components are more toxic than others. A summary of the studies funded under the NPACT initiative is provided in Table 1.

HEI funded two major NPACT studies under RFA 05-1-A, which combined coordinated efforts in (1) exposure assessment using advanced techniques, (2) epidemiology focusing on PM components and long-term health effects, and (3) toxicology focusing on endpoints that are relevant to the cardiovascular and other health effects observed in epidemiologic studies. Each main study comprised several studies, led by co-investigators, looking at different aspects of the questions regarding the cardiovascular and other health effects of short- and long-term exposure to PM components, using exposure assessment, epidemiologic approaches, and toxicologic approaches that would complement each other.

The two major NPACT studies were led by Dr. Morton Lippmann at New York University and Dr. Sverre Vedal at the University of Washington. Dr. Lippmann's study comprised two toxicologic studies led by Drs. Lung-Chi Chen and Terry Gordon and two epidemiologic studies led by Drs. Kazuhiko Ito and George Thurston. Dr. Vedal's study comprised an epidemiologic study of two cohorts, as described below, and a toxicologic study conducted by Drs. Matthew Campen at the University of New Mexico and Jacob McDonald at the Lovelace Respiratory Research Institute (LRRI).

At the time of funding for the two integrated NPACT studies, HEI was already supporting a time-series epidemiologic study of PM components by Dr. Michelle Bell at Yale University (RFA 04-2, *Walter A. Rosenblith New Investigator Award*). Because the topic was very relevant to the NPACT initiative, HEI decided to include this study under the broader umbrella of NPACT (although the study was reviewed separately and published earlier).

OVERSIGHT AND REVIEW OF THE NPACT STUDIES

Given the complexity of the NPACT studies, the HEI Research Committee formed an NPACT Oversight Committee composed of Research Committee members and additional technical experts. The Oversight Committee met approximately annually with the investigator teams during the conduct of the study and provided advice and feedback on the study design, analytical plans, and progress. The Oversight Committee members are listed on the Contributors page.

In addition, HEI formed an NPACT Advisory Group, which included representatives from the U.S. EPA and industry sponsors of the NPACT studies, as well as other interested stakeholders. The advisory group met with the NPACT investigators to discuss study designs, progress, and other key issues.

Given the breadth and depth of the two major NPACT studies, HEI convened a special NPACT Review Panel, chaired by members of the HEI Review Committee and comprising twelve experts in medicine, epidemiology, toxicology, statistics, atmospheric chemistry, and exposure. The members of the Panel were not involved in either conducting or overseeing the studies, and they subjected the studies to intensive peer review. The Panel and HEI scientific staff then produced the detailed Commentaries published in the reports to discuss the strengths and weaknesses of the studies, as well as the relevance of the findings to major air quality public health policy questions.

Table 1. HEI's NPACT Studies

RFA / RFP[a] Investigator (Institution)	Study or Report Title	Citation or PI
RFP December 2003: To Create a Database of Air Pollutant Components		
Christian Seigneur (AER)	Creation of an Air Pollutant Database for Epidemiologic Studies	*https://hei.aer.com*
RFA 04-2: Walter A. Rosenblith New Investigator Award		
Michelle Bell (Yale University)	Assessment of the Health Impacts of Particulate Matter Characteristics	Bell 2012
RFA 05-1-A: Conducting Full Studies to Compare Characteristics of PM Associated with Health Effects		
Morton Lippmann (New York University)	National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of Particulate Matter Components	
	NPACT Study 1. Subchronic Inhalation Exposure of Mice to Concentrated Ambient $PM_{2.5}$ from Five Airsheds	Chen
	NPACT Study 2. In Vitro and In Vivo Toxicity of Exposure to Coarse, Fine, and Ultrafine PM from Five Airsheds	Gordon
	NPACT Study 3. Time-Series Analysis of Mortality, Hospitalizations, and Ambient $PM_{2.5}$ and Its Components	Ito
	NPACT Study 4. Mortality and Long-Term Exposure to $PM_{2.5}$ and Its Components in the American Cancer Society's Cancer Prevention Study II Cohort	Thurston
Sverre Vedal (University of Washington)	National Particle Component Toxicity (NPACT) Initiative Report on Cardiovascular Effects. Section 1. NPACT Epidemiologic Study of Components of Fine Particulate Matter and Cardiovascular Disease in the MESA and WHI-OS Cohorts	Vedal
	National Particle Component Toxicity (NPACT) Initiative Report on Cardiovascular Effects. Section 2. NPACT Animal Toxicologic Study of Cardiovascular Effects of Mixed Vehicle Emissions Combined with Non-vehicular Particulate Matter	Campen
RFA 05-1-B: Conducting Planning or Demonstration Studies to Design a Major Study to Compare Characteristics of PM Associated with Health Effects		
JoAnn Lighty (University of Utah)	A planning study to investigate the impacts of dust and vehicles on acute cardiorespiratory responses in the arid Southwest.	Lighty et al. 2008 (unpublished report)

[a] RFA indicates request for applications; RFP, request for proposals.

STUDY BY LIPPMANN ET AL.

Approach

Lippmann and colleagues at New York University conducted four toxicologic and epidemiologic studies to determine short- and long-term health effects associated with PM and its components. Study 1, led by Lung-Chi Chen, analyzed heart rate variability (HRV) and atherosclerosis in mice exposed for 6 months by inhalation to fine concentrated ambient particles (CAPs) in five geographic regions in the United States. Study 2, led by Terry Gordon, measured acute changes in markers of inflammation and oxidative stress in mice and human cell lines exposed to a large number of PM samples collected at the same five locations as in the Chen study, focusing on metal composition and PM size classes (coarse, fine, and ultrafine). Study 3, led by Kazuhiko Ito, used data from the U.S. EPA's CSN in a time-series analysis of all-cause mortality and hospital admissions associated with specific source categories of $PM_{2.5}$ in 150 U.S. cities. Study 4, led by George Thurston, also used CSN data to evaluate associations between long-term exposure to PM components and mortality from cardiovascular disease (CVD), respiratory disease, and lung cancer for participants in the Cancer Prevention Study II (CPS-II) maintained by the American Cancer Society.

Lippmann and colleagues used source apportionment techniques to evaluate which specific components and source categories might be contributing most to the health effects associated with exposure to PM. Studies 1, 2, and 3 used basic factor analysis, whereas Study 4 used absolute principal component analysis to further apportion $PM_{2.5}$ mass to the source categories.

Results and Interpretation

Study 1 Chen and Lippmann observed that mice exposed to CAPs for 6 months showed greater plaque development in the arteries than mice exposed to filtered air at Manhattan and Tuxedo, New York, and East Lansing, Michigan. In contrast, no differences between the control and CAPs-exposed mice were seen at Seattle, Washington, and Irvine, California. They found that CAPs exposures were associated with acute increases in heart rate and decreases in HRV at Manhattan and, to a lesser extent, at Tuxedo. Very few significant associations for HRV were seen at the other locations. The investigators concluded that the effects on plaque progression were most likely attributable to a Coal Combustion source category, and that the Residual Oil Combustion, Coal Combustion, and Traffic source categories contributed most to the observed acute cardiac effects.

In its independent review, the HEI NPACT Review Panel noted that the results of Study 1 are consistent with evidence from earlier studies that exposure to CAPs leads to acute changes in heart rate and HRV, as well as chronic changes in atherosclerotic plaques and markers of inflammation. Presumably, the effects observed at Tuxedo resulted from long-range transport of pollutants from other areas. Surprisingly, few changes were observed at Seattle and Irvine, two major urban areas dominated by traffic-related pollution. The Panel was not persuaded by the investigators' interpretation that the Residual Oil and Coal Combustion source categories were the most important contributors to health effects, however. It remains unclear to what extent the larger responses observed in some locations might have reflected higher CAPs exposures, rather than differences in PM composition. There is also uncertainty in assigning source categories in the factor analyses and it remained unclear why plaque progression in mice exposed to CAPs at Seattle and Irvine was the same as that in mice exposed to filtered air.

Study 2 Gordon and colleagues observed small differences in the production of reactive oxygen species (ROS) in human epithelial and endothelial cell lines according to location, season, and size fraction, with the highest ROS production for samples from Manhattan and Los Angeles. ROS responses to ultrafine PM samples from all sites were higher than responses to coarse and fine PM samples (on an equal mass basis); responses were higher in summer for fine and ultrafine samples but higher in winter for coarse samples. Strong correlations were observed between ROS production and copper, antimony, vanadium, cobalt, beryllium, and nickel. The investigators observed an increase in neutrophils, a sign of inflammation, in the lungs of PM-exposed mice. They noted a larger neutrophil response to the coarse fraction of PM than to the fine and ultrafine fractions, but those changes did not correlate well with in vitro ROS production for the same PM sample. The investigators concluded that the composition of PM samples pointed to the Traffic and Residual Oil Combustion source categories as contributors to the observed effects.

The Panel noted that Gordon and colleagues had conducted a large and systematic effort to evaluate the relative toxicity of PM samples and found some differences according to size fraction, season, and location. However, the Panel thought that the differences were relatively small and therefore the possible toxicity of any particular components or size classes could not be ruled out. A limitation of the study is that it did not evaluate any organic carbon (OC), elemental carbon (EC), or other organic components of PM.

Study 3 Ito and colleagues evaluated associations between PM components or source categories and daily deaths and hospital admissions in 150 U.S. cities and in a subset of 64 cities for which data on both PM components and gaseous pollutants were available. In city-specific analyses, they reported many associations across a variety of statistical models, although associations with individual $PM_{2.5}$ components were not particularly consistent. The most consistent associations were with total $PM_{2.5}$ mass itself and with the Traffic source category. However, the Panel noted that this could be in part because $PM_{2.5}$ was measured more frequently than its components were, and Traffic was more often identified as a source category than were other categories. In nationwide analyses, significant associations were observed most consistently between all-cause mortality and sulfate, weekday excess $PM_{2.5}$, lead, and carbon monoxide; between cardiovascular hospitalizations and copper, nickel, and vanadium; and between respiratory hospitalizations and copper, nitrogen dioxide, and silicon. In two-pollutant analyses, the inclusion of total $PM_{2.5}$ in the models with the individual components in many cases appeared to decrease the effect estimates.

The Panel noted that results of Study 3 support associations of daily mortality and hospital admissions with both traffic-related pollutants and secondary aerosols. The Panel emphasized that some results should be interpreted with caution because a high proportion of the data for important PM components (e.g., nickel, arsenic, copper, and vanadium) was below the limit of detection or had low monitor-to-monitor correlations. The patterns of correlations between pollutants were complicated and it was difficult to interpret their potential effects on associations with health effects.

Study 4 In this cohort study, Thurston and colleagues found the strongest associations for mortality with the Coal Combustion and Traffic source categories and with sulfur, which strongly contributed to both source categories, and EC, the primary contributor to Traffic. The associations of Traffic and EC with mortality were, however, highly sensitive to the inclusion of ecologic covariates in the analyses

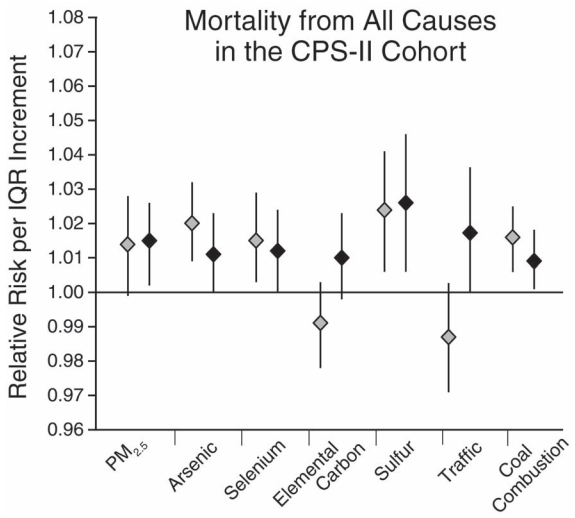

Figure 1. Relative risks of mortality from all causes in the CPS-II cohort associated with $PM_{2.5}$ and selected components and factors. Results presented are those that demonstrated the most consistently positive associations; the remaining results were not positive or significant. Gray and black diamonds depict results from the random effects Cox models without and with contextual ecologic covariates, respectively. Note that the IQR (interquartile range) varied by pollutant; e.g., the IQRs for $PM_{2.5}$ and sulfur were 3.13 μg/m^3 and 0.53 μg/m^3, respectively.

and to the use of a random effects Cox model instead of a standard Cox proportional hazards model (see Figure 1). The investigators concluded that long-term exposure to $PM_{2.5}$ and the Coal Combustion source category explained most of the associations of exposure to $PM_{2.5}$ with all-cause, ischemic heart disease, and lung cancer mortality (but not respiratory mortality).

The Panel noted that Study 4 yielded many interesting results during the extended follow-up period of the CPS-II cohort. However, the Panel was not convinced that the study has definitively demonstrated that long-term exposure to components of $PM_{2.5}$ is more important than exposure to total $PM_{2.5}$ in causing adverse effects. Although the Panel agreed that the investigators found the most consistent associations with the Coal Combustion source category, the Panel disagreed with the investigators' conclusion that exposure to coal combustion emissions is more strongly associated with mortality than exposure to traffic emissions, because traffic is one of the most important contributors to within-city differences in $PM_{2.5}$ exposure; however, this is not well captured by the limited number of monitors within a city. The Panel also noted other issues, such as a decreasing trend in coal combustion emissions over the past decades.

Although the Total Risk Index analysis provided some interesting results that suggested that exposure to combinations of components and gases in pollutant mixtures is potentially more toxic than exposure to $PM_{2.5}$ mass alone, the Panel thought that the approach, although promising, had some problems that precluded considering these results to be more than suggestive.

Conclusions

Lippmann and colleagues conducted a comprehensive research program to evaluate the relative toxicity of $PM_{2.5}$ components and source categories. The findings identified Coal Combustion, Residual Oil Combustion, Traffic, and Metals source categories as most consistently associated with health effects. However, the Panel thought that the study has not shown conclusively that specific components or sources were more definitively associated with health outcomes than other components or sources.

STUDY BY VEDAL ET AL.

Approach

Vedal and colleagues at the University of Washington hypothesized that the cardiovascular health effects associated with long-term exposure to $PM_{2.5}$ are driven in large part by traffic-related sources. They used data from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Women's Health Initiative–Observational Study (WHI-OS) cohorts. The MESA cohort comprised approximately 6800 participants (45 to 84 years old) living in six U.S. cities. Endpoints evaluated were two subclinical markers of atherosclerosis, carotid intima-media thickness (CIMT) and coronary artery calcium (CAC), measured at baseline and follow-up visits. The WHI-OS cohort comprised approximately 90,000 postmenopausal women (50 to 79 years old) living in 45 U.S. cities. Outcomes included deaths from total CVD and from atherosclerotic and cerebrovascular disease (including stroke), as well as time to the first event (fatal and nonfatal) associated with CVD, including coronary heart disease and stroke.

The investigators obtained concentrations for $PM_{2.5}$, sulfur, OC, EC, and silicon (used as markers for specific source categories) from the U.S. EPA's CSN. They then estimated long-term pollutant concentrations to which participants in both cohorts had been exposed (referred to as the *national spatial model*). They also used data from additional measuring campaigns in the MESA cities to estimate spatially and temporally resolved concentrations at the participants' residences in the MESA cohort (referred to as the *spatiotemporal model*). The investigators conducted source apportionment, primarily to assist in interpreting the $PM_{2.5}$ component health effect estimates.

In a parallel toxicologic study, Matthew Campen of the University of New Mexico and colleagues at LRRI evaluated the role of mixed vehicular engine emissions (MVE) and its gaseous components in contributing to adverse health effects of PM. They generated a mixture of diesel and gasoline emissions and exposed mice that are prone to developing atherosclerotic plaques to whole MVE or MVE gases only (i.e., without PM). They also generated primary sulfate, nitrate, and fine road dust and exposed the mice to combinations of such non-vehicular PM and

MVE or MVE gases. They then assessed biomarkers of oxidative stress and vascular inflammation in the exposed mice. Campen and colleagues used multiple additive regression tree (MART) analysis to evaluate associations between the hundreds of compounds measured in the generated atmospheres and various biologic markers.

Results and Interpretation

MESA Study Vedal and colleagues reported that CIMT was significantly associated with exposure to $PM_{2.5}$, OC, and sulfur in both the spatiotemporal and national spatial models, although the risk estimates were generally small (see Figure 2). The relative risks for OC and sulfur were higher than for $PM_{2.5}$ for the spatiotemporal model, but in the national spatial model this was true only for the city-adjusted model for sulfur. The investigators reported no significant associations of CAC with $PM_{2.5}$ in any model. When the spatiotemporal model of exposure was used in an analysis adjusted for city, relative risks for sulfur, EC, and OC became significant. In the analyses using the national spatial model, the relative risk of OC was elevated, and the relative risks for sulfur, EC, and OC were significant in the city-adjusted analyses.

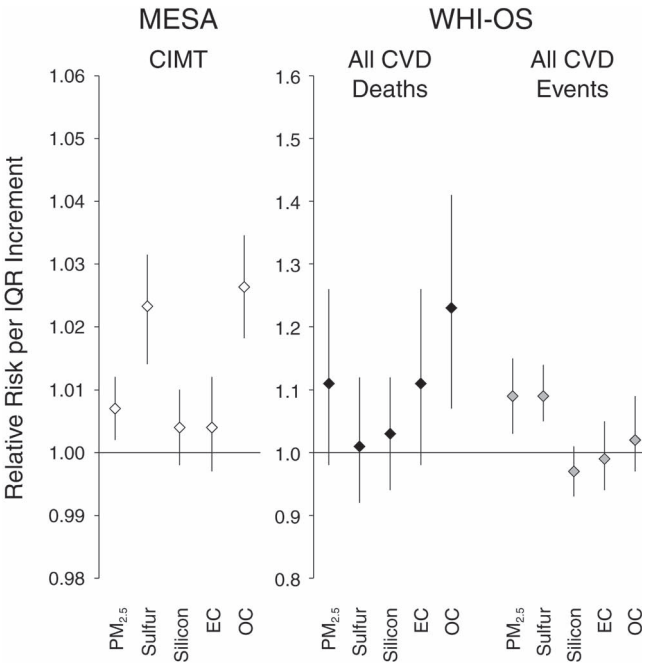

Figure 2. Associations found between selected pollutants and carotid intima-media thickness (CIMT) in the MESA cohort (left) and total cardiovascular disease mortality or events in the WHI-OS cohort (right). Data shown are relative risk estimates with 95% confidence intervals associated with an interquartile range (IQR) increment of baseline exposure using spatiotemporal model predictions (Model 3) for MESA data and national spatial model predictions for WHI-OS data. Note that the IQR varied by study, by pollutant, and by exposure model — for example, the IQRs for $PM_{2.5}$ and sulfur were 3.9 μg/m^3 and 0.25 μg/m^3, respectively, in WHI-OS and 1.51 μg/m^3 and 0.51 μg/m^3, respectively, in MESA. Also note differences in the *y*-axis scales.

In its independent review of the study, the HEI NPACT Review Panel commented that the analysis of subclinical cardiovascular effects is a promising direction for air pollution epidemiology. However, the Panel noted that the longitudinal analyses of CAC and CIMT (i.e., over several follow-up visits) were hampered by the short period of time between evaluations, leaving only the cross-sectional evaluation (i.e., at one time point across cities) with interpretable results. Furthermore, the Panel thought that the spatiotemporal model did not fully represent the spatial variability of locally variable components such as EC, which may have further resulted in a lack of associations. Overall, the Panel thought that further follow-up of the MESA cohort would be useful, including analyses of subclinical endpoints that were not covered in the current study (e.g., markers of inflammation and coagulation and other biomarkers).

WHI-OS Study Vedal and colleagues reported that total deaths from CVD and from atherosclerotic disease showed the strongest associations with OC; associations with $PM_{2.5}$ and EC were marginal (see Figure 2). Associations between deaths from cerebrovascular disease and exposure to OC were significant but less strong; they were not significant for $PM_{2.5}$ or any of the other components. Associations of total CVD events with $PM_{2.5}$ and sulfur were statistically significant, although small; a negative and marginal association was found for silicon. The only significant associations for coronary heart disease events were with sulfur and $PM_{2.5}$. Cerebrovascular disease events were significantly associated with OC and with $PM_{2.5}$ and marginally associated with sulfur. A significant negative association was observed with silicon. Additional analyses to compare the relative contributions of within- and between-city variances found mixed results.

The Panel noted that the WHI-OS study was well conducted and included a wide set of cardiovascular outcomes, including cerebrovascular outcomes and non-fatal events. The Panel was not surprised that this study found that the regionally varying pollutants — sulfur and OC — were more prominently associated with outcomes than more locally variable pollutants, such as EC. However, the Panel cautioned that nonsignificant results for such locally variable pollutants are not evidence of a lack of associations, given the study design and high correlations between components (particularly, EC and OC). Overall, the Panel thought that the WHI-OS study had produced interesting results but that the data could be further explored with more locally focused exposure modeling strategies.

Exposure Assessment The Panel thought that the four components of interest were logical choices and that the focus on these markers was justified. The source apportionment provided reassurance that the selected components generally covaried with the factors, as expected,

although none was unequivocally linked to vehicle emissions, which limited the investigators' ability to assess the importance of traffic sources in the two cohorts.

The multiple exposure estimates used in the MESA study provided a good opportunity to gain new insight into how the choice of exposure model affected the results. The Panel noted that the ability of the models to predict national-scale patterns does not necessarily translate into an ability to predict patterns within a city and that developing a reliable model is generally more difficult for within-city patterns.

Toxicologic Study Campen and colleagues reported that lipid peroxidation, a marker of oxidative stress, was increased in aortic tissue of mice exposed to various atmospheres, with the largest increase observed after exposure to MVE. Removing the particles from the atmosphere reduced these effects but did not fully eliminate them. In contrast, exposures to non-vehicular PM alone did not produce an effect. Infiltration of atherosclerotic plaques by macrophages increased after exposure to MVE and to MVE gases combined with either sulfate or nitrate. In contrast, plaque formation increased only after exposure to nitrate alone or nitrate combined with MVE gases, but not to the other atmospheres. The investigators reported less consistent changes in the other endpoints.

The Panel noted that Campen and colleagues had conducted a complex study with an impressive number of single and combined exposure atmospheres. The results suggested that the PM in MVE played a significant role in the induction of aortic lipid peroxidation, more so than MVE gases. These findings differ from those of previous studies from this laboratory, which found that the gaseous components in diesel or in gasoline exhaust induced oxidative stress. However, in the absence of exposures using MVE particles alone (i.e., without the gases), the role of MVE particles by themselves remains unclear.

Several caveats suggest a cautious interpretation of these results, including possible variability in aortic tissues because of sample collection procedures, small group sizes for certain endpoints resulting in insufficient power to find an effect, and some subjectivity in the method for assessing plaque densities. The Panel thought that the MART analysis was an interesting approach but that the interpretation remains limited because the number of independent atmospheres was small compared with the number of components measured and because daily variability in composition was not assessed.

Conclusions

The epidemiologic study by Vedal and colleagues has added to the evidence about long-term exposure to particulate air pollution and cardiovascular events and mortality, although the relative importance of traffic versus other sources of PM remains unclear. Given the often high correlations among pollutants and the multiple sources of some components, interpretations about specific components and sources remain limited. The results of the toxicologic study support the notion that both particulate and gaseous components of vehicle exhaust play a role in the induction of various cardiovascular outcomes.

STUDY BY BELL

Dr. Bell evaluated short-term effects of PM components on mortality in 187 counties across the United States (as reported in her study *Assessment of the Health Impacts of Particulate Matter Characteristics* [2012]). She was one of the first researchers to make use of the data that would later make up the CSN database, and she applied the time-series approach developed in the National Morbidity, Mortality, and Air Pollution Study (Samet et al. 2000) to look for associations between PM component concentrations and mortality and morbidity outcomes. Bell obtained data on $PM_{2.5}$ total mass and on the mass of 52 chemical components of $PM_{2.5}$ for air monitored in 187 counties in the continental United States for the period 2000 through 2005. She also collected data on daily admissions to hospitals for cardiovascular- and respiratory-related illnesses for the period 1999 through 2005 for Medicare enrollees 65 years or older. She began by characterizing how the chemical composition of $PM_{2.5}$ varies regionally and seasonally in the United States. Subsequently, she evaluated whether the associations between short-term exposure to PM total mass and health effects followed regional and seasonal patterns, and whether the observed effects could in turn be explained by regional and seasonal variations in the chemical composition of $PM_{2.5}$ (Bell 2012).

SYNTHESIS OF THE NPACT INITIATIVE

As outlined above, HEI funded the NPACT initiative to provide more insight into which components of the PM mixture may be responsible for its toxicity and human health effects. The initiative consisted of coordinated epidemiologic and toxicologic studies conducted in multiple cities to evaluate the toxicity of different chemical and physical properties of PM and their associated health effects, while taking into account the contribution of gaseous copollutants. The NPACT initiative has spanned nearly a decade from its initial conception and the development of RFA 05-1, through the issuing of the RFA and study selection, to the conduct of research, submission of the final reports, and evaluation by the HEI NPACT Review Panel. It is important to take a broad look at the results of all the separate epidemiologic and toxicologic studies that were part of the two major research efforts and to consider them in the context of current scientific understanding of how particle components may affect health, and to what sources those components can be attributed.

This Synthesis section looks broadly at the approaches and results of the reports by Dr. Morton Lippmann at New York University (hereafter referred to as the Lippmann team, study, or report) and Dr. Sverre Vedal at the University of Washington (hereafter referred to as the Vedal team, study, or report). In this section, the HEI NPACT Review Panel considers whether there is coherence and consistency in the epidemiologic and toxicologic results and discusses the larger scientific significance of the overall findings and their implications for future research into the health effects of particle components.

DATA AND STUDY DESIGN

In addition to its detailed reviews of each study as described in the respective Commentaries accompanying each report, the NPACT Review Panel considered, and discusses here, some of the strengths and limitations encountered by both teams in the design of the studies, the availability of data, exposure assessment and exposure atmosphere generation, and possible approaches to linking PM components to specific sources. Table 2 summarizes the various studies that were conducted by the two teams of investigators.

PM Composition Data

Both the Lippmann and the Vedal epidemiologic studies relied on PM composition data available from the CSN, operated by the U.S. EPA, which to date is the most comprehensive effort in the world to systematically collect such data nationwide. In addition, the Vedal team augmented the CSN data with their own monitoring data. Although these studies could not have been undertaken without the availability of the CSN data, the Panel noted that they also highlight some of the limitations of that network. First, the network is relatively sparse, comprising only about 200 locations nationally, such that the finer-scale spatial gradients in chemical components within cities are not captured. Second, although taking samples more often than many other efforts to collect PM component data, most CSN locations collect samples only once every three or six days. This infrequency limits researchers' ability to evaluate associations of PM components with daily

Table 2. Broad Overview of NPACT Study Designs[a]

Study Approach	Lippmann et al.	Vedal et al.
Exposure timescales	Short- and long-term	Long-term only
Health endpoints	Respiratory and cardiovascular	Cardiovascular only
Epidemiologic Studies		
Study design	Multicity time-series analysis and one cohort	Two cohorts
Health endpoints	Acute: respiratory and cardiovascular mortality and hospitalizations Chronic: mortality	Chronic: Subclinical markers of atherosclerosis; cardiovascular disease events (including mortality)
PM components and exposure assessment	EPA CSN monitors; MSA averages; sources	Cohort-specific and EPA CSN and IMPROVE monitors; individual-level exposure predictions; two exposure models; focus on OC, EC, silicon, and sulfur; included some evaluation of other pollutants and PM components
Source apportionment goal	Assessing exposure	Interpretation of exposure health effect estimates
Toxicologic Studies		
Study design	ApoE knockout mouse model (normal diet); 6-month exposures; FVB/N mice; 12-day and 100-day exposures	ApoE knockout mouse model (high-fat/high-cholesterol diet); 50-day exposure
Biologic endpoints	Cardiovascular effects and markers of oxidative stress and inflammation	Vascular effects and markers of oxidative stress and inflammation
Animal and cell culture exposures	Concentrated ambient particles (in vivo) and ambient particles collected on filters (in vitro and in vivo); five air sheds	Laboratory-generated complex mixtures: combinations of mixed vehicle emissions and non-vehicular primary particles (in vivo)

[a] ApoE indicates apolipoprotein E; CSN, Chemical Speciation Network; EC, elemental carbon; EPA, U.S. Environmental Protection Agency; IMPROVE, Interagency Monitoring of Protected Visual Environments; MSA, metropolitan statistical area; OC, organic carbon; PM, particulate matter.

health outcomes in short-term study designs and (to a lesser extent) reduces the information available for long-term averaging in the longer cohort studies. Third, concentrations of many of the components measured in the CSN network, especially metals, are below their minimum detection limits (MDLs) on a large number of sampling days, limiting analyses to only those components that can be detected repeatedly and reliably. Fourth, the accuracy of measured concentrations of EC and OC depends on the methods used to measure these components. Because the measurements are defined operationally (EC and OC are complementary fractions of total carbon, and their respective concentrations depend on the methods used for sampling and measuring carbonaceous material), there is considerable uncertainty associated with them, and comparing them across studies is difficult. These issues affect some of the chemical components most important to the NPACT studies.

The Vedal team addressed the sparseness of the monitoring network and non-continuous sampling by adding extra monitors in additional locations to measure EC, OC, and the other PM components measured by the CSN and by calculating average concentrations over longer (2-week) time periods. However, the Panel noted that they did not use the same measurement approach in their additional monitoring as was employed by the CSN, and their results did not agree well with measurements from collocated CSN monitors. Thus, although the increased spatial information provided by the additional monitoring might have reduced exposure measurement error, the different approach and sampling time used by the additional monitoring campaign might have actually enhanced such error.

In particular, the Panel considered the uncertainties in EC and OC measurements important because these components are used to help identify traffic as a source of PM. The Vedal team focused on these components in accordance with their hypothesis that traffic-related air pollutants drive the effects of PM on health. Source apportionment analyses conducted by the Lippmann team were also sensitive to these two components, because they were used in the estimation of traffic-related source categories. In addition to being operationally defined (see above), EC and OC are known to be subject to strong spatial and temporal gradients, making it likely that the small number of observations made at central monitoring stations do not adequately represent the highly variable concentrations observed across an entire urban area. Nonetheless, EC and OC continue to be important components to characterize in studies that evaluate the health impacts of PM components, particularly when there is an interest in traffic-related effects.

On the other hand, sulfate (measured as elemental sulfur) is well captured by the CSN. Sulfur concentrations are typically well above detection limits, are measured with relatively high certainty, and have relatively low spatial variability. Therefore, exposure measurement error associated with sulfate is expected to be low. Selenium, arsenic, vanadium, and nickel, which are key components for identifying coal-burning and fuel-oil combustion, are often below the limit of detection in the CSN database. The low concentrations of those pollutants, which have been decreasing over the past decades, hinder assessment of how they might be linked to health impacts. However, as reported by the Lippmann team in the current and prior studies, in some locations (notably New York City) concentrations of vanadium and nickel are sufficiently high that it has been possible to identify associations of these elements with health outcomes. New local regulations in New York City that address fuels used for residential heating are expected to reduce concentrations of nickel and vanadium in ambient air.

Linking PM Components and Sources to Health Outcomes

For their epidemiologic analyses, the two NPACT teams adopted somewhat different philosophies on the use of source apportionment to link health outcomes to PM components. The Lippmann team relied heavily on a source apportionment approach that they had developed previously to link source categories directly to health outcomes in their epidemiologic analyses, whereas the Vedal team used source apportionment to assist in the interpretation of their health effects estimates and to support their focus on OC, EC, silicon, and sulfur as markers of specific sources in their analyses of health outcomes. An underlying question is which approach provides better information about which sources of PM components most affect health risks: Is it better to use source apportionment results, which may represent more accurately the combined effects of multipollutant atmospheres, but which require more effort and introduce additional uncertainties and assumptions, or is it better to simply use individual components that are typically linked to one or more specific sources? Each approach has its strengths, and there are strong reasons to use either method or both methods (as was done by the Lippmann team).

The Panel noted that all current source apportionment approaches (see the Source Apportionment sidebar in the Commentary accompanying each report) introduce uncertainty (Balachandran et al. 2012). Although some approaches may decrease uncertainty by reducing temporal variability, other approaches that produce source categories may increase temporal variability as compared with approaches using concentrations of individual components. For some approaches those potential errors can be quite large. In their analyses using an approach based on factor analysis methods that they had developed previously, the Lippmann team found differences among locations in terms of which components contributed to similar source categories, providing indications that source emissions vary

spatially, that the factor analytic approaches are sensitive to measurement uncertainties, that there are temporal variations in the composition of the emissions, and that other factors may add uncertainty to this approach. Two of the limitations noted by the Panel were that the investigators did not account for how uncertainties in the component measurements affect the certainty of the source categories and that many of the concentrations were below the MDL. How their results might differ from those obtained using a different source apportionment technique and what the effect would have been of including measurement uncertainties and MDLs in the analyses remain unknown. Furthermore, it is not apparent which chemical components drive the associations between source categories and key health outcomes in the Lippmann report (which is a different issue from determining which components are contained in the source categories that they identified). It was reassuring, however, that the Lippmann team came to consistent interpretations when they did include individual components in their analyses. We refer readers to the Commentary in HEI Research Report 177 for a more detailed discussion of these issues.

The Vedal team applied positive matrix factorization (PMF), a widely used source apportionment approach, to support their focus on EC, OC, silicon, and sulfur as key components in their analyses of health outcomes. The Panel thought that their approach was defensible. The PMF factors they identified were reasonably consistent with what was expected in terms of sources and were also generally consistent with the source apportionment results of the Lippmann team. However, it would be of interest to compare the PMF results of the Vedal team directly with the source apportionment results of the Lippmann team in those cities that the two studies had in common.

The Panel thought that the question of how (or whether) to use source apportionment to identify which PM components have strong associations with adverse health outcomes is an important one. It is generally preferable to use both source categories and component concentrations directly in the health analyses, if the study design permits, with a focus on examining consistencies and differences between the two approaches. When source apportionment results are used for health analyses, researchers should recognize, discuss, and — if possible — address the uncertainties introduced by this method.

Estimating Exposure Using Air Quality Data

The Lippmann team approached the estimation of exposure from measured air pollutant concentrations in a straightforward fashion; they assumed that the monitored concentrations (or source apportionment results estimated for each city based on a single monitor or a few central monitors) can be used directly, with little additional spatial modeling to account for spatial gradients (e.g., variation due to different land uses and activities). The Vedal team, on the other hand, developed a more elaborate spatiotemporal exposure model, which estimated exposures at the individual level (i.e., the outdoor concentrations at participants' residences) for the MESA cohort. This approach was made possible by the intensive, dedicated monitoring conducted by the team in the six cities of the MESA study. The Vedal team also constructed a national spatial exposure model, which also estimated component concentrations at participants' homes for their analyses of both the MESA cohort and the WHI-OS cohort.

The Panel thought that the initial formulation of the approach by the Vedal team was promising. However, the Panel noted that there were challenges associated with estimating EC and OC concentrations at the individual level. For instance, there were only small differences between EC concentrations measured at roadside locations and those at urban background locations, raising questions about the ability of the spatiotemporal model to accurately assign exposure at participant residences. The Panel identified additional concerns with the approach used by the Vedal team (as discussed in the Commentary accompanying the Vedal report, HEI Research Report 178), such as the varying R^2 values for the different components across the models (an indication of model accuracy in model validation) and the potential loss of volatile components over the longer sampling period of 2 weeks. At the same time, the Panel noted the more general challenge facing the primary alternative to such spatiotemporal modeling, which is the reliance on observations from just a few sites to characterize potential populationwide intra-urban exposures to pollutants such as EC, OC, and other primary pollutants (in much the same way the Lippmann team proceeded). Although using one or a few sites to characterize individual and populationwide exposures to certain secondary PM components, such as sulfate, may be sufficiently accurate, using this approach to estimate exposures to primary pollutants — such as metals — introduces larger uncertainties, potentially biasing the results.

Single-Pollutant and Multipollutant Models

When associations of $PM_{2.5}$ components and health outcomes are analyzed in single-pollutant models, potential interactions or high correlations between components could affect the analysis and lead to misidentification of which pollutants may be most strongly associated with the observed human and animal health effects. Furthermore, other constituents of inhaled atmospheres — such as gaseous pollutants — might complicate assessment of which associations may be causally related. The Lippmann team attempted to address these issues by employing source apportionment in all of their studies, two-pollutant models in time-series analyses in which they controlled for $PM_{2.5}$ mass, and a total-risk-impact approach in their cohort study. The Vedal team made simple comparisons between the results for individual components and those

for $PM_{2.5}$ mass in their epidemiologic study and carried out sensitivity analyses involving two-pollutant models. They performed a more sophisticated analysis (i.e., a MART analysis) in their toxicologic study (the Campen study), in which they related the hundreds of compounds measured in their complex exposure atmospheres to biologic markers. Although the Panel appreciated the efforts of both NPACT teams, they concluded that any future research using PM component data needs to more directly address appropriate analyses for multipollutant atmospheres in the statistical design.

Approaches to Animal Inhalation Exposures

The two NPACT teams exposed apolipoprotein E (ApoE) knockout mice to exposure atmospheres with pollutant concentrations that were by design higher than typical North American ambient concentrations, although such concentrations can be found in developing countries or occupational settings. The teams used different approaches to generate the pollutant mixtures, making it possible to compare responses to concentrated ambient PM and predetermined laboratory mixtures in a similar animal model. The Lippmann team (specifically the Chen study) used concentrators that pass ambient air through a cyclone that excludes particles larger than 2.5 µm, and then through a virtual impactor that concentrates particles between about 0.1 and 2.5 µm. The system does not exclude (or concentrate) gaseous pollutants or particles smaller than 0.1 µm (ultrafine PM). Thus, the resulting CAPs exposure atmosphere is similar in pollutant composition to the ambient air, but the mixture is altered in terms of both particle concentration and relative composition. The Panel noted that this is an appropriate approach given the focus on PM components in the NPACT initiative and the fact that much of the mass of ambient PM is within the size range ($PM_{2.5}$) that is being concentrated and of great interest regarding its health effects. The approach used by the Vedal team in their toxicologic study (conducted at LRRI) was to generate controlled atmospheres by mixing diluted and cooled exhaust from a gasoline and a diesel engine to provide a base pollutant mixture (i.e., MVE) and then removing PM from the mixture or adding different types of PM. This approach was driven by their general focus on PM components derived from traffic (vehicular) sources for both the epidemiologic and toxicologic studies. The Lippmann team measured about 30 components in the CAPs atmospheres, whereas LRRI measured close to 500 compounds (metals and many organic compounds in the particle and gas phases) in their complex exposure atmospheres.

The inhalation exposures at LRRI did not include secondary PM components that are formed by atmospheric processes (e.g., secondary organic aerosols). However, sulfate and nitrate ions, which are major PM components in ambient air, were added as primary particles, allowing the team to investigate the health effects of exposure to those components. In a typical city, secondary sulfate particles would form by oxidation of gaseous sulfur dioxide emissions from coal or oil burning, whereas secondary nitrate particles would be formed by oxidation of nitrogen oxides emitted by vehicles and other combustion sources. A unique feature of the Campen study was the addition of road dust particles in the fine fraction. In contrast, the animal exposure atmospheres used in the Chen study included secondary aerosols by design, although the extent to which this occurred likely varied by location (the West Coast of the United States versus the East Coast versus the Midwest). Exposure mixtures for both studies contained PM: at LRRI, from engine emissions or added nitrate, sulfate, and road dust; for the Lippmann study, from general traffic sources. Gaseous pollutants in engine exhaust were included or excluded by design at LRRI, and ambient gaseous pollutants were present by default (but not concentrated) in the CAPs exposures in the Chen study. In addition to the animal inhalation exposures in the two studies, the Lippmann team also used intratracheal aspiration of particles collected on filters (in the Gordon study), which allowed them to investigate the differences in biologic responses in mice exposed to different PM size ranges. This approach excluded gaseous components altogether. The investigators analyzed endotoxin content of the filter samples and elemental composition, but did not analyze OC, EC, or other organic compounds.

Because the Lippmann team did not use specific source mixtures for the exposures but conducted inhalation studies in five locations with different ambient air pollution mixtures, they conducted source apportionment to link their exposures back to source categories, such as emissions from mobile and stationary sources. Therefore, the animal exposure strategies of both teams had the potential to link biologic endpoints to similar types of sources, such as traffic, power generation, and dust, as well as to secondary aerosols (sulfates and nitrates). Furthermore, the parallel epidemiologic studies used similar markers for mobile-source emissions (EC and OC), although the source apportionment methods typically used in epidemiologic studies encounter difficulties in separating PM derived from gasoline engines from PM derived from diesel engines based on EC and OC concentrations.

The Panel thought that MVE was a reasonable representation of mobile source emissions for toxicologic studies that allowed a more direct comparison of the toxicologic results with epidemiologic results for non-source-specific estimates of traffic-related exposures. On the other hand, the sulfate added to the MVE exposures at LRRI was a primary rather than secondary particle and did not include other components (e.g., selenium, arsenic, vanadium, or nickel) that are often found in emissions from sources that emit sulfur dioxide, and was thus less representative of real-world conditions.

COMPARING KEY FINDINGS ACROSS THE STUDIES

This section discusses the main findings in terms of what sources and PM components the teams found to play a role in the health outcomes they assessed, looking for consistency across the epidemiologic and toxicologic studies within and across the two main NPACT studies. Overviews of the main findings of the epidemiologic and toxicologic studies are presented in Tables 3 and 4, respectively.

The Lippmann team's time-series study (the Ito study) identified a fairly large number of PM components associated with daily hospitalizations due to CVD and daily all-cause and CVD mortality. Source categories attributed to primary vehicle exhaust and secondary sulfate aerosols were found to be important in some of these short-term associations. The long-term American Cancer Society cohort study (the Thurston study) also identified a number of PM components that could explain some of the mortality associations, including EC and sulfur. However, OC, silicon, and potassium (a marker for biomass combustion) were not associated with mortality in the cohort study. Source categories attributed to coal combustion and traffic pollution were found to be important in the associations with long-term effects, whereas little evidence was found for associations with source categories attributed to crustal sources or biomass combustion. There was minimal overlap between the $PM_{2.5}$ components associated with short-term responses and those associated with long-term responses. Results for metals varied, but many effect estimates were highly uncertain (i.e., the confidence intervals were large), possibly due to the limited number of measurements above the limit of detection for metallic components in many cities.

The Vedal epidemiologic study focused primarily on EC and OC as markers of vehicle exhaust and other combustion emissions, on OC also as a marker of secondary organic aerosol, on silicon as a marker of crustal PM, and on sulfur as a marker of secondary PM. Results suggested that OC and sulfur were associated with several of the endpoints studied, but EC and silicon were not. The Panel agreed with the investigators that this suggests that traffic-related pollution and secondary PM could be playing a role in PM toxicity.

The Lippmann team's animal inhalation study (the Chen study) showed that a large number of components were positively or negatively associated with acute changes in heart rate and HRV in mice. When the investigators tried to rank these components, they concluded that nickel, aluminum, EC, phosphorus, and sulfur had stronger associations with the cardiac endpoints than did $PM_{2.5}$ mass. Effects of CAPs exposures on plaque progression in mice were primarily seen at Tuxedo, Manhattan, and East Lansing, where the investigators deemed pollution mixtures to be more influenced by coal-fired power plant emissions than at Irvine, and Seattle. The Lippmann team's in vitro and in vivo study of PM collected on filters (the Gordon study) found that PM size and composition (determined by location and season) played a complex role in PM toxicity. The Panel noted that no size classes or components could be ruled out.

The toxicologic study conducted at LRRI (the Campen study) used laboratory-generated atmospheres based on MVE and MVE gases combined with non-vehicular PM. Several combinations of particles and gases were found to affect different biologic markers in aortic tissues. The whole MVE mixture produced the largest changes, with MVE gases producing smaller and fewer changes. Fewer effects were observed with primary nitrate and sulfate particles, and none with fine road dust particles. Combining non-vehicular PM with MVE gases increased the effects over non-vehicular PM alone, but generally did not exceed the effects of MVE by itself. Thus there was little evidence of a more-than-additive effect when exposure atmospheres were combined. The results support the role of both particulate and gaseous components in the induction of various cardiovascular outcomes, but whether there are important particle–gas interactions remains unclear and requires further research.

REFLECTIONS ON THE MAIN FINDINGS

Both the Lippmann and Vedal studies found that adverse health outcomes were consistently associated with sulfur and sulfate (markers primarily of coal and oil combustion) and with traffic-related pollutants, although the relative importance of the latter remains unclear because exposure to traffic-related pollutants varies within metropolitan areas and thus is more subject to uncertainty than exposure to pollutants from other source categories. On the other hand, there were only small differences in EC concentrations measured at roadside locations compared with urban background locations, indicating either spatial homogeneity in concentrations or, as noted above, potentially high measurement error for EC due to the 2-week sampling protocol. The results for sulfur and sulfate may have been more consistent because their concentrations were more accurately estimated (due to their spatial homogeneity) than concentrations of other pollutants.

Biomass combustion, crustal sources, and related components were not generally associated with short- or long-term epidemiologic findings in these studies, but there were only a few cities where these sources (and their attributed components) were likely to be measured consistently. The possibility remains that biomass combustion contributed to OC concentrations, and thus to the associations reported for OC and cardiovascular outcomes. There were few consistent associations with other components or sources, although the Panel cautioned that is not conclusive evidence that these components and sources do not have

Table 3. Approaches and Key Findings of the Epidemiologic Studies[a,b]

	New York University / Ito		New York University / Thurston	University of Washington / Vedal[c]			
Study design	Time series (short-term)		Cohort (long-term)	Cohort (long-term)		Cohort (long-term)	
Population	U.S. MSAs		ACS CPS-II cohort	MESA		WHI-OS	
Cities	150 cities		100 cities	6 cities		45 cities	
Participants	Population >100 million		~450,000 people	~6,800 people		~90,000 people	
Health endpoints	Hospitalization	Mortality	Mortality	CIMT	CAC	Time to first event (MI, stroke, cardiac procedures, and CVD deaths)	Mortality
PM components and source categories associated with health outcomes	Cold season: $PM_{2.5}$, NO_2, CO, EC, OC, and Cu Modified[d] by $PM_{2.5}$: Cu, Ni, and V Sources: vehicle exhaust	Warm season: $PM_{2.5}$, NO_3, and sulfate Modified[d] by $PM_{2.5}$: sulfate Sources: secondary aerosols	Components: $PM_{2.5}$, As, Se, sulfur, Cl, Fe, Pb, and EC Not associated: OC, silicon, and K Source categories: coal combustion and possibly traffic; little evidence for soil or biomass combustion	Best evidence for OC and sulfur; little evidence for EC or silicon; some evidence for Cu	Some evidence for OC only	Best evidence for sulfur and less for OC; little evidence for EC or silicon	Best evidence for OC and less for sulfur; little evidence for EC or silicon

[a] ACS CPS-II indicates American Cancer Society Cancer Prevention Study II; As, arsenic; CAC, coronary artery calcification; Cl, chlorine; CIMT, carotid intima-media thickness; CO, carbon monoxide; Cu, copper; CVD, cardiovascular disease; EC, elemental carbon; Fe, iron; K, potassium; MESA, Multi-Ethnic Study of Atherosclerosis; MI, myocardial infarction; MSA, metropolitan statistical area; Ni, nickel; NO_2, nitrogen dioxide; NO_3, nitrate; OC, organic carbon; Pb, lead; PM, particulate matter; $PM_{2.5}$, particulate matter ≤ 2.5 µm in aerodynamic diameter; Se, selenium; V, vanadium; WHI-OS, Women's Health Initiative–Observational Study.

[b] Epidemiologic studies at New York University were headed by George Thurston and Kazuhiko Ito and at the University of Washington by Sverre Vedal.

[c] Source apportionment results supported the focus on four main components for evaluation in the Vedal study: EC and OC as markers of vehicle exhaust and other combustion emissions; OC also as a marker of secondary organic aerosol; silicon as a marker of crustal PM; and sulfur as a marker of secondary PM.

[d] Risk estimates for these components were substantially modified when $PM_{2.5}$ was included in a two-pollutant model.

Table 4. Approaches and Key Findings of the Toxicologic Studies[a,b]

	New York University / Chen		New York University / Gordon		University of Washington / Campen
Study design	Short-term (daily time-series)	Long-term (6 months)	Short-term (12 days)	Long-term (100 days)	Medium-term (50 days)
Exposures	Inhalation of CAPs at five locations (Manhattan, Tuxedo, East Lansing, Seattle, and Irvine)		Aspiration of PM collected on filters at five locations (Manhattan, Tuxedo, Ann Arbor, Seattle, and Los Angeles area); three size fractions		Inhalation of combinations of MVE or MVE gases with non-vehicular $PM_{2.5}$ (sulfate, nitrate, or road dust)
PM concentrations	60–138 µg/m^3		In vitro: 50–100 µg/mL In vivo: 50 µg		100 or 300 µg/m^3
Model	ApoE knockout mice (normal diet)		FVB/N mice; epithelial cells, endothelial cells, cardiomyocytes	FVB/N mice	ApoE knockout mice (high-fat/high-cholesterol diet)
Biologic endpoints	Heart rate and heart rate variability	Aorta plaque growth; serum biomarkers; heart rate and heart rate variability	Mice: lung inflammation Cells: viability, ROS, inflammatory markers, beat frequency	Lung inflammation	Aorta: lipid peroxidation, vascular function and remodeling, plaque growth and inflammation
PM components and sources associated with biologic findings	Effects after exposure to Ni (residual oil combustion) > to Al, EC, and P (traffic) > to sulfur (coal combustion) > to $PM_{2.5}$	Plaque growth in Tuxedo, Manhattan, and East Lansing, but not in Irvine and Seattle; attributed to coal combustion	Complex interaction of particle size and composition (location and season); nothing ruled out	Source apportionment not reported	Effects after exposure to MVE > to MVE gases; fewer effects of nitrate and sulfate; no effects of road dust Effects after exposure to non-vehicular PM combined with MVE > non-vehicular PM without MVE

[a] Al indicates aluminum; CAPs, concentrated ambient particles; MVE, mixed vehicular engine emissions; Ni, nickel; P, phosphorus; PM, particulate matter; ROS, reactive oxygen species.

[b] Toxicologic studies at New York University were headed by Lung-Chi Chen and by Terry Gordon and for the University of Washington study by Matthew Campen at the University of New Mexico and Jacob McDonald at the Lovelace Respiratory Research Institute.

adverse health effects. Further analyses of some of these sources are warranted.

With regard to the association of health effects with EC compared with those associated with OC, the differences in findings between the Lippmann and Vedal studies are surprising. In typical urban environments, mobile sources are expected to be the major source of EC and important contributors to OC. It is noteworthy that these studies report such prominent differences between the results for EC and OC, given the strong correlation between the two in many cities. Again, these differences may be due to the stronger spatial gradients between cities for OC than for EC, the exposure models and study designs, or the difficulties involved in measuring OC and EC.

One limitation of the CSN is that it is by design focused on $PM_{2.5}$, while it is becoming increasingly clear that coarse PM remains of interest. For example, the Lippmann team's in vitro and in vivo toxicologic evaluations (in the Gordon study) found stronger associations per unit mass between coarse PM, which is often associated with dust, and certain biologic endpoints than for fine PM. However, associations of silicon, a marker for dust, with health effects or clinical markers in the epidemiologic studies were often fairly weak (with the exception of CIMT in the Vedal epidemiologic study), as would be expected.

Both studies highlight how important the CSN is to research on the health effects of components of air pollution and to air quality management. Neither study could have been performed without CSN data, although the studies highlighted some limitations that suggest that further efforts would be helpful to characterize EC, OC, and metals (i.e., combustion- and traffic-related components); to lower the detection limits of some components; and to collect daily measurements. In summary, the Panel concluded that — except for the fairly consistent associations of many of the health outcomes with sulfur and sulfate, which may, in part, be due to better exposure assessment — associations with other components were mixed, and linkages to sources were not definitive.

How do these two major studies compare with the published literature? Quite a few investigators have performed smaller-scale studies and analyses to identify which PM components and sources are associated with a variety of adverse health outcomes. Not surprisingly, the results of those studies have been mixed, if only because of the differences in the selection of PM components and health outcomes of interest, study time frames (short- and long-term), and the imprecision of estimates because of the difficulties in obtaining truly large data sets on PM composition and sources.

In the third NPACT study, Bell (2012) used daily Medicare hospitalization data to evaluate the effects of short-term exposures to various components of the $PM_{2.5}$ mixture on daily morbidity. She focused on the average values of seven $PM_{2.5}$ components (those accounting for $\geq$ 1% of $PM_{2.5}$ mass in the CSN) in 187 U.S. counties, using national, regional, and seasonal models. For her all-year analysis of the entire United States, Bell reported strong and statistically significant increases in the association between cardiovascular hospitalizations and an interquartile range increase in EC, nickel, and vanadium (Bell 2012).

It is beyond the scope of this Executive Summary to provide a detailed review of the literature on the health effects of PM components and sources. A recent systematic review of the findings of animal toxicology, human chamber, and field epidemiology studies (Stanek et al. 2011) presents results from five epidemiologic studies on total mortality (see Table 3 of that paper), which among them found that soil, sea salt, local sulfur dioxide, secondary sulfate, motor vehicle emissions, coal burning, wood smoke, biomass combustion, copper smelter emissions, residual oil combustion, and incinerator emissions were associated with health outcomes. This is just one illustration of the variety of results reported in the literature.

Together, the two studies discussed here, as well as the study by Bell, follow the conclusion of Stanek and colleagues (2011) that "apportionment methods have linked a variety of health effects to multiple groups of PM components and sources of PM, but the collective evidence has not yet isolated factors or sources that would be closely and unequivocally related to specific health outcomes."

Overall, this comprehensive and ambitious research program has shown that research on the toxicity of PM components is not likely to easily identify a single culprit PM component or source category or to identify a unique set of biomarkers that could be reliably used to monitor exposure. More work remains to be done to refine statistical methods for simultaneous modeling of multiple pollutants; to improve the representation of spatial contrasts in component concentrations, especially within cities; and to improve source identification and attribution. Further toxicologic studies are needed to connect particle components with physiologic mechanisms, to study the relative toxicity of particles and gaseous pollutants, to study atmospheric aging of complex mixtures to better reflect real-world conditions, and to provide more insight into the role of $PM_{2.5}$ components in causing tissue injury and dysfunction.

The NPACT studies, which are to date the most systematic effort to combine epidemiologic and toxicologic analyses of these questions, found associations of secondary sulfate and, to a somewhat lesser extent, traffic sources with health effects. But the Panel concluded that the studies do not provide compelling evidence that any specific source, component, or size class of PM may be excluded as a possible contributor to PM toxicity. If greater success is to be achieved in isolating the effects of pollutants from mobile and other major sources, either as individual

components or as a mixture, more advanced approaches and additional measurements will be needed so that exposure at the individual or population level can be assessed more accurately. Such enhanced understanding of exposure and health will be needed before it can be concluded that regulations targeting specific sources or components of $PM_{2.5}$ will protect public health more effectively than continuing to follow the current practice of targeting $PM_{2.5}$ mass as a whole.

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ABBREVIATIONS AND OTHER TERMS

AER	Atmospheric and Environmental Research
ApoE	apolipoprotein E
CAC	coronary artery calcium
CAPs	concentrated ambient particles
CIMT	carotid intima-media thickness
CPS-II	Cancer Prevention Study II
CSN	Chemical Speciation Network
CVD	cardiovascular disease
EC	elemental carbon
HRV	heart rate variability
LRRI	Lovelace Respiratory Research Institute
MART	multiple additive regression tree
MDL	minimum detection limit
MESA	Multi-Ethnic Study of Atherosclerosis
MVE	mixed vehicular engine emissions
NPACT	National Particle Component Toxicity (initiative)
OC	organic carbon
PM	particulate matter
$PM_{2.5}$	particulate matter ≤ 2.5 μm in aerodynamic diameter
PMF	positive matrix factorization
RFA	request for applications
RFP	request for proposals
ROS	reactive oxygen species
U.S. EPA	U.S. Environmental Protection Agency
WHI-OS	Women's Health Initiative–Observational Study

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