



# STATEMENT

Synopsis of Research Report 178

HEALTH  
EFFECTS  
INSTITUTE

## National Particle Component Toxicity (NPACT) Initiative Report on Cardiovascular Effects

### BACKGROUND

Extensive epidemiologic evidence, as well as toxicologic evidence, supports an association between air pollution and adverse health effects, in particular cardiovascular disease (CVD). Because detailed insight is needed into whether certain components of the particulate matter (PM) mixture may be responsible for its toxicity and human health effects, HEI funded the National Particle Component Toxicity (NPACT) initiative. The initiative consisted of coordinated epidemiologic and toxicologic studies to evaluate the relative toxicity of various chemical and physical properties of PM and selected gaseous copollutants. The lead investigators were Drs. Sverre Vedal (for this report) and Morton Lippmann (for HEI Research Report 177). Given the strong associations between ambient PM concentrations and cardiovascular mortality and morbidity, the NPACT studies focused primarily on health outcomes and biologic markers related to CVD.

### APPROACH

Vedal and colleagues at the University of Washington hypothesized that the cardiovascular health effects associated with long-term exposure to PM<sub>2.5</sub> (PM with an aerodynamic diameter  $\leq 2.5 \mu\text{m}$ ) 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

### What This Study Adds

- Vedal and colleagues' coordinated epidemiologic and toxicologic studies of the cardiovascular effects of PM components, with a focus on traffic sources, are an important addition to air quality and health research. In their study, they evaluated data from the MESA and WHI-OS cohorts and exposed mice to combinations of mixed vehicular engine emissions and non-vehicular PM.
- The investigators found strong evidence for associations of PM<sub>2.5</sub>, 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 exhaust and to a lesser extent exhaust gases on vascular markers in mice; non-vehicular PM induced few effects.
- The study has added to the evidence about long-term exposure to particulate air pollution and cardiovascular events and mortality, although the relative importance of traffic sources remains unclear. Because pollutant concentrations are often correlated, interpretations about specific components and sources remain limited.

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<sub>2.5</sub>, sulfur, organic carbon (OC), elemental carbon (EC), and silicon (used as markers for specific source categories) from the U.S. Environmental Protection Agency's Chemical Speciation Network (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 *spatio-temporal model*). The investigators also conducted source apportionment, primarily to assist in interpreting the PM<sub>2.5</sub> component health effect estimates.

In a parallel toxicologic study, Matthew Campen of the University of New Mexico and colleagues at the Lovelace Respiratory Research Institute evaluated the role of mixed vehicular engine emissions (MVE) and its gaseous components in contributing to the 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

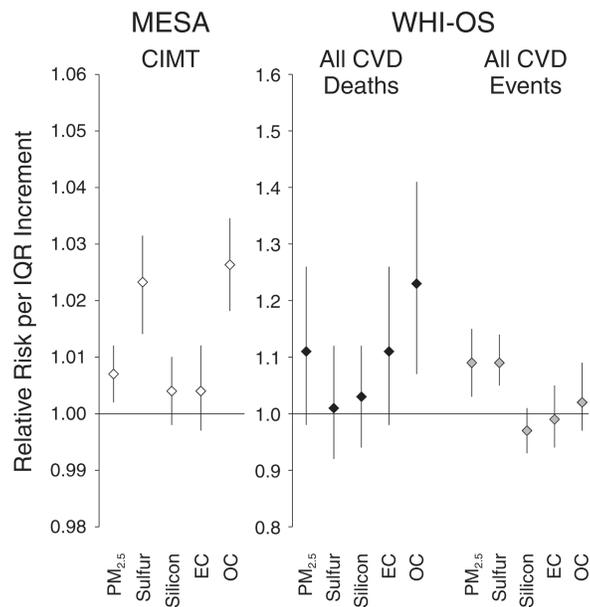
**MESA Study** Vedal and colleagues reported CIMT was significantly associated with exposure to PM<sub>2.5</sub>, OC, and sulfur in both the spatiotemporal and national spatial models, although the risk estimates were generally small (see Figure). Relative risks for OC and sulfur were higher than for PM<sub>2.5</sub> 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<sub>2.5</sub> 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 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.

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<sub>2.5</sub> and EC were marginal (see the Figure). Associations between deaths from cerebrovascular disease and exposure to OC were significant but less strong; they were not significant for PM<sub>2.5</sub> or any of the other components. Associations of total CVD events with PM<sub>2.5</sub> 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<sub>2.5</sub>. Cerebrovascular disease events were significantly associated with OC and PM<sub>2.5</sub> 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



**Figure.** 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<sub>2.5</sub> and sulfur were 3.9 µg/m<sup>3</sup> and 0.25 µg/m<sup>3</sup>, respectively, in WHI-OS and 1.51 µg/m<sup>3</sup> and 0.51 µg/m<sup>3</sup>, respectively, in MESA. Also note differences in the y-axis scales.

— 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.

### **SYNTHESIS OF NPACT STUDIES BY LIPPMANN AND VEDAL**

This section looks broadly at the approaches and results of the reports by Drs. Lippmann and Vedal and considers whether there is coherence and consistency in the epidemiologic and toxicologic results.

Both 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. 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 limited number of cities where these sources and components were likely to be measured consistently. The possibility remains that biomass combustion contributed to OC

concentrations and thus to its associations with cardiovascular outcomes. There were few consistent associations with other components or sources, although the Panel cautioned that this is not conclusive evidence that these components and sources do not have adverse health effects. Further analyses of some of these sources are warranted.

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.

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 effects will be needed before it can be concluded that regulations targeting specific sources or components of PM<sub>2.5</sub> will protect public health more effectively than continuing to follow the current practices of targeting PM<sub>2.5</sub> mass as a whole.