HEALTH EFFECTS INSTITUTE

# STATEMENT

Synopsis of Research Report 177

# NPACT: Particulate Matter Components Associated with Health Effects

## BACKGROUND

Extensive epidemiologic evidence, as well as toxicologic evidence, supports an association between air pollution exposure and adverse health effects, in particular cardiovascular disease (CVD). In order to gain an insight as to 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. Morton Lippmann (this report) and Sverre Vedal (HEI Research Report 178). Given the well documented 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

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 in 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. Environmental Protection Agency's Chemical Speciation Network (CSN) in a time-series analysis of all-cause mortality and hospital admissions associated with specific source categories of PM ≤ 2.5 µm in aerodynamic diameter ($PM_{2.5}$) 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 CVD,

### What This Study Adds

- In this comprehensive and ambitious study, Lippmann and colleagues performed coordinated epidemiologic and toxicologic studies of the health effects of PM and its components. They conducted studies in mice and in human cell lines exposed to ambient PM and epidemiologic studies of short- and long-term cardiovascular effects. These studies mark an important addition to research on air quality and health.
- This 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.
- 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 practices of targeting $PM_{2.5}$ mass as a whole.

This Statement, prepared by the Health Effects Institute, summarizes a research project funded by HEI and conducted by Dr. Morton Lippmann at New York University Medical Center, Tuxedo, NY, and colleagues. The complete report, *National Particle Component Toxicity (NPACT) Initiative: Integrated Epidemiologic and Toxicologic Studies of the Health Effects of Particulate Matter Components* (© 2013 Health Effects Institute), can be obtained from HEI or our Web site (see last page).

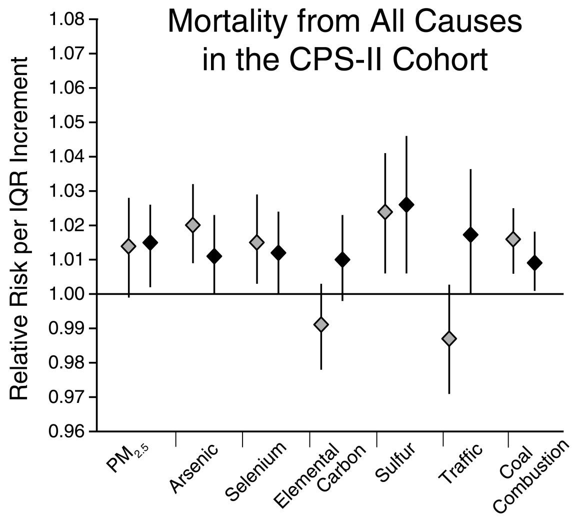
respiratory disease, and lung cancer for participants in the Cancer Prevention Study II (CPS-II) cohort maintained by the American Cancer Society.

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; 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 Combustion 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 remains unclear why plaque progression in mice exposed to CAPs at Seattle and Irvine was the same as that in mice exposed to filtered air.




**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 $\mu g/m^3$ and 0.53 $\mu g/m^3$, respectively.

***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 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 the 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 of those 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 and to the use of a random effects Cox model instead of a standard Cox proportional hazards model (see the figure). 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 important 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.

## 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 cautions 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 does not play a role in 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 $PM_{2.5}$ will protect public health more effectively than continuing to follow the current practice of targeting $PM_{2.5}$ mass as a whole.

HEALTH EFFECTS INSTITUTE

101 Federal Street, Suite 500
Boston, MA 02110, USA
+1-617-488-2300 phone
+1-617-488-2335 fax

*pubs@healtheffects.org*
*www.healtheffects.org*