HEI Perspectives 3

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Insights from HEI's research

Understanding the Health Effects of Ambient Ultrafine Particles

HEI Review Panel on Ultrafine Particles

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 this project, the preparation and publication of this document was partially supported by the Federal Highway Administration.

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.

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.

EXECUTIVE SUMMARY

Understanding the Health Effects of Ambient Ultrafine Particles

INTRODUCTION

Over the past 30 years, a large body of scientific literature has emerged that provides evidence of associations between short-term and long-term exposures to ambient particulate matter (PM) and increased mortality and hospitalization from cardiovascular and respiratory diseases. Most of the evidence is based on epidemiologic studies of human exposure to PM with aerodynamic diameters ≤ 10 micrometers (PM_{10}) or ≤ 2.5 micrometers ($PM_{2.5}$). However, scientists and regulators have long known that PM in the ambient air is a complex mixture including particles of different sizes and chemical composition. What has been less clear is whether certain characteristics of the ambient mixture are more harmful to public health than others and are therefore the most important to control. In its 1998 blueprint for a research program on airborne PM, the United States National Research Council identified improved understanding of ultrafine particles (UFPs) as a priority.

UFPs make up the smallest size fraction in what is a continuum of airborne particles with diameters ranging from a few nanometers to several micrometers. By convention, UFPs have been defined as particles that are 100 nanometers or less in diameter (≤100 nm). Given their small size, UFPs contribute little to the mass of PM in ambient air, but they are the dominant contributors to particle number. Motor vehicles, especially those powered by diesel engines, have often been cited as a leading source of ambient UFP emissions and of human exposure.

Concern about UFPs developed from early evidence, primarily from animal and in vitro studies, that suggested that they could be inhaled more deeply into the lung and might be more toxic than larger particles. The first epidemiologic studies that included particle number measurements also suggested that UFPs might be associated with the same adverse effects in humans that have been attributed to larger particle size fractions. Scientists hypothesized that UFPs would have greater toxicity than larger particles in part because their vast numbers and small diameters mean that they have a high surface area, a potentially important interface through which to transmit any toxic chemicals that might be adsorbed.

In the decades since concerns were first raised about UFPs, the role they might play in the adverse health effects associated with exposures to air pollution has remained an important research target at institutions around the world, including HEI. National and local air quality authorities in the United States and in other regions of the world continue to assess the need for specific action on UFPs in reviews of ambient air quality standards and other regulatory programs. At the same time, under existing regulatory and technological changes, UFP emissions from motor vehicles are already changing. The resulting impacts on ambient concentrations, and ultimately on human exposures, are difficult to predict.

TIME FOR A BROAD PERSPECTIVE

Given this context, HEI formed a special panel (see Contributors list) to review the scientific evidence available on UFPs and to present its evaluation in this third issue of the HEI Perspectives series: *Understanding the Health Effects of Ambient Ultrafine Particles.*

The Panel structured its assessment of the scientific evidence regarding ambient UFPs as responses to three questions:

- Ambient UFPs — sources, emissions, and exposures: To what extent do motor vehicles contribute? (Chapter 2);
- Do UFPs affect health? What is the evidence from experimental studies in animals and humans? (Chapter 3);
- Do UFPs affect human health at environmental concentrations? What is the evidence from epidemiologic studies? (Chapter 4).

Chapter 2 explores the contribution of motor vehicles within the broader context of the multiple sources of ambient UFPs. It discusses in detail the changing profiles of mobile-source emissions, the spatial and temporal patterns of ambient UFP concentrations, and the implications of all these factors for the design and interpretation of studies of UFP exposure and health.

The next two chapters explore the health evidence on UFP exposures from a broad array of study designs using animal and human subjects. Chapter 3 focuses on the evidence from

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experimental studies in animals and in humans because they can directly test hypotheses about the causal role of specific exposures.

Chapter 4 focuses on observational epidemiologic studies of people exposed to UFPs in the environment, in mostly urban settings. Because they involve studies of people exposed to concentrations of air pollutants found in the real world, epidemiologic studies of UFPs have the potential to provide more direct evidence with which to determine whether UFPs affect human health at concentrations found in the environment.

Chapters 3 and 4 both focus on various measures of intermediate markers and health endpoints that represent the multiple hypothesized pathways for UFP effects. Most of these pathways are shared by PM generally, but some pathways may be especially relevant for UFPs.

In identifying experimental and epidemiologic studies for its assessment, the Panel made a number of choices to make sure that responses to the questions were most informed by studies relevant to the understanding of the potential risks of inhaling ambient UFPs, particularly those related to motor vehicle exhaust. For the experimental studies, it considered only studies involving exposures to UFPs via the inhalation route, which is physiologically relevant and directly comparable with the results of epidemiologic studies. The Panel therefore excluded in vitro studies or studies in which particles were directly instilled into the lungs or airways. The Panel focused on exposures to combustion-related UFPs and therefore largely excluded the vast literature on engineered nanoparticles. The Panel also placed particular emphasis on both experimental and epidemiologic studies of UFPs that included analyses of exposures to copollutant gases and larger particle size fractions, because of the potential of such studies to provide insight into the role of UFPs themselves in any health effects observed.

Finally, Chapter 5 summarizes each chapter's main conclusions and attempts to identify some of the broader lessons, about both the specific health effects associated with exposures to UFPs and possible directions for future studies that could enhance our understanding of emissions, exposures, and effects of UFPs.

SUMMARY AND CONCLUSIONS

A substantial body of literature has now been published on the sources of UFPs, their spatial and temporal distribution in ambient air, their inhalation and fate in the body, their mechanisms of toxicity, and their adverse effects in animals and in humans. The purpose of this issue of HEI Perspectives is to provide a broad assessment of what has been learned about UFPs and what remains poorly understood. The Panel's findings in response to the three questions posed at the outset of this Executive Summary are summarized briefly below.

AMBIENT UFPs — SOURCES, EMISSIONS, AND EXPOSURES: TO WHAT EXTENT DO MOTOR VEHICLES CONTRIBUTE?

As products of combustion and secondary atmospheric transformations, ambient UFPs have multiple sources whose relative contributions to ambient concentrations vary with location, season, and time-of-day. However, in urban areas, particularly in proximity to major roads, motor vehicle exhaust can be identified as the major contributor to UFP concentrations. Diesel vehicles have been found to contribute substantially, sometimes in disproportion to their numbers in the vehicle fleet.

However, the absolute and relative contributions of different vehicle types to motor vehicle emissions are changing rapidly. On the one hand, under the force of regulations to reduce particle mass and number emissions from diesel and other vehicles, the emissions, and therefore ambient levels, of UFPs will decrease. On the other hand, this decrease may be partially offset by UFP emissions from the growing use of certain types of gasoline direct injection technology to boost fuel efficiency. The role that will be played by new fuels, such as ethanol and biodiesel blends and natural gas, remains largely ill-defined. The collective effect of all these changes has not been thoroughly explored and will likely vary regionally, depending on the rate and extent to which they are deployed in different parts of the world.

It has been more challenging to characterize human exposure to ambient UFPs than to the more regionally dispersed and routinely monitored pollutants, such as $PM_{2.5}$. UFP concentrations are highly variable spatially, declining rapidly with distances from roadways, for example, such that UFPs often differ substantially from one location to another within the same city. Given their small contribution to mass, UFPs are not well reflected in PM mass measurements and they are not routinely monitored in most locations. Studies of UFPs have relied on a variety of detection methods, most commonly measures of number concentration. In addition, UFPs are highly correlated with other combustion-related pollutants, such as carbon monoxide and nitrogen oxides. These correlations must be taken into account when evaluating exposure to sources such as traffic, or when designing epidemiologic studies and interpreting their results. Reliance on measurements at central-site monitors to represent broad population exposure — a central feature in epidemiologic studies of long-term exposures to $PM_{2.5}$ and other pollutants — is likely to lead to errors in estimates of exposure to UFPs.

Despite the high spatial variability of UFPs, the UFP number concentrations measured at multiple locations within cities do tend to be reasonably correlated in time, rising and falling in similar patterns over the course of a day. Moderately high temporal correlations between UFP number concentrations at central monitors, outdoors at residences, and even indoors at residences have been observed in some, but not all, cities. The correlations are not always as strong as those observed for $PM_{2.5}$, but in some locations they can be sufficient to support epidemiologic studies on the effects of short-term variations of number concentrations on human health, using study designs that have been employed for larger particle size fractions. However, the temporal variability in UFP number concentration can be similar to that of other PM size fractions and gaseous pollutants, making it difficult to differentiate the effects of UFP number concentration in such study designs.

DO UFPs AFFECT HEALTH? WHAT IS THE EVIDENCE FROM EXPERIMENTAL STUDIES IN ANIMALS AND HUMANS?

Experimental studies have provided a rationale for the hypothesis that the adverse health effects of exposure to UFPs differ from those of larger particles. As a result of their physical characteristics, inhaled UFPs differ from larger particles in their deposition patterns in the lung, their clearance mechanisms, and in their potential for translocation from the lung to other tissues in the body. Some animal studies have also demonstrated translocation of UFPs via the olfactory nerve to the brain.

Both animal and human studies provide evidence for respiratory and cardiovascular effects associated with exposure to UFPs. Observed effects in selected studies include lung function changes, airway inflammation, enhanced allergic responses, vascular thrombogenic effects, altered endothelial function, altered heart rate and heart rate variability, accelerated atherosclerosis, and increased markers of brain inflammation. Largely, with the exception of brain effects, the findings are similar to those observed for exposures to fine particles.

While selected studies show evidence for UFP effects, the current evidence, when considered together, is not sufficiently strong to conclude that short-term exposures to UFPs have effects that are dramatically different from those of larger particles. There are limitations and inconsistencies in the findings from short-term studies on UFP health effects, and there are no long-term animal exposure studies of UFP health effects. Relatively few studies have directly compared UFPs with other particle size fractions. These factors constrain our ability to draw definitive conclusions about the specific consequences of exposure to UFPs.

DO UFPs AFFECT HUMAN HEALTH AT ENVIRONMENTAL CONCENTRATIONS? WHAT IS THE EVIDENCE FROM EPIDEMIOLOGIC STUDIES?

A growing number of epidemiologic studies conducted over roughly the past 10 years have evaluated impacts of UFPs. These studies have provided suggestive, but often inconsistent, evidence of adverse effects of short-term exposures to ambient UFPs on acute mortality and morbidity from respiratory and cardiovascular diseases. One explanation that must be considered for the results to date is weakness in the true underlying relationship between UFP exposures and adverse effects — that the null hypothesis being tested by these studies is true. However, limitations of the current studies are likely to play a role; UFPs have not been assessed routinely in large epidemiologic studies of air pollution health effects, in part because ambient monitoring of UFPs has not been conducted in most locations or has not been done with the same measurement techniques. As a result, studies tend to be smaller and the likelihood of exposure measurement error tends to be greater for UFPs relative to $PM_{2.5}$ and other pollutants; both of these factors reduce statistical power to test confidently for what may be small but important health outcomes.

The available observational study designs have also not been able to clearly determine whether UFPs have effects independent of those for related pollutants. Where studies have measured UFPs, few have assessed whether the effects associated with UFPs are independent of other pollutants. When they have, the effects of UFPs have not been consistently discernible from those of other pollutants with which they often occur or share similar sources (e.g., traffic). Of 42 articles published since 1997 that cited any significant health associations with UFPs measured as number concentration, 37 articles also noted significant effects for other particle size fractions or traffic-related pollutants, and 10 articles did not consider any traffic-related gases in the analysis.

No epidemiologic studies of long-term exposures to ambient UFPs have been conducted. This is because the most common epidemiologic study designs for long-term exposures are dependent on spatial contrasts in concentrations that have been more difficult to characterize for UFPs than for $PM_{2.5}$.

OVERALL CONCLUSIONS

Airborne PM has been the focus of extensive research and debate in the United States and around the world for several decades. Considerable evidence from a broad array of experimental and epidemiologic studies has led to strong scientific consensus on the independent associations of airborne PM, in particular $PM_{2.5}$ and PM_{10}, with adverse respiratory and cardiovascular effects on human health. This evidence has provided the foundation for many regulatory decisions to limit both PM emissions, including those from motor vehicles, and ambient PM concentrations to which people might be exposed.

What role have ambient concentrations of UFPs played in the adverse effects that have been observed in human populations exposed to ambient air pollution?

Several factors — the unique physical properties of UFPs, their interactions with tissues and cells, their potential for translocation beyond the lung — have led scientists to expect that UFPs may have specific or enhanced toxicity relative to other particle size fractions and may contribute to effects beyond the respiratory system. However, the considerable body of research that has been conducted has not provided a definitive answer to this question. Toxicologic studies in animals, controlled human exposure studies, and epidemiologic studies to date have not provided consistent findings on the effects of exposures to ambient levels of UFPs, particularly in human populations. The current evidence does not support a conclusion that exposures to UFPs alone can account in substantial ways for the adverse effects that have been associated with other ambient pollutants such as $PM_{2.5}$.

The fact that the current database of experimental and epidemiologic studies does not support strong and consistent conclusions about the independent effects of UFPs on human health does not mean that such effects, as one part of the broader effects attributable to $PM_{2.5}$, can be entirely ruled out. There are limitations in the evidence base attributable to underlying deficiencies in exposure data, to numerous challenges in comparing and synthesizing results of existing studies, and to the inherent complexity of the task that scientists have set out to accomplish.

WHERE DO WE GO FROM HERE?

There are many considerations beyond the scientific opinions expressed in this issue of HEI Perspectives that inform the level of confidence in the evidence necessary for policy makers to "ensure that resources spent in the future on control technology and regulatory compliance will have a reasonable probability of success" (U.S. National Research Council 1998). Among them is the need to weigh carefully the value to scientific understanding and to regulatory decisions of continuing to treat UFPs as an individual pollutant versus alternative approaches that focus on the health effects of exposure to traffic or to the broader air pollution mixture.

As part of that discussion, this report lays out possible research steps toward addressing some of the limitations of the current evidence on the specific role of UFPs. Experimental study designs could include controlled exposures to UFPs and related copollutants in studies that replicate key animal research results on effects beyond the lung (e.g., in the cardiovascular and central nervous systems), that extend analyses to other animal species and disease models, and that involve long-term exposures. Epidemiologic studies could include more carefully targeted designs that exploit contrasts in ambient UFP exposures but that improve the ability to characterize the independent effects of exposure to UFPs, more consistent and comparable study designs that would support meta-analyses, and designs that permit assessment of the impacts of long-term exposures. Ultimately, many of the underlying challenges posed by the existing evidence on ambient UFPs relate to limitations in characterization and analysis of exposure, so recommendations for exploration of alternative exposure metrics, spatial modeling techniques, and statistical methods are also included.

Regardless of the evidence for a specific role for UFPs, many of the recent PM regulatory decisions affecting fuels, engine designs, and exhaust aftertreatment in countries around the world are likely to result in significant reductions in emissions of both fine and ultrafine particles. The time course of these and other changes in the emissions of UFPs or their precursors and their impact on ambient concentrations will depend on a number of factors, including shifts in the size, age, and composition of the vehicle fleet in particular regions. Monitoring and evaluation of such changes will be essential in the years to come; without them, questions will remain about whether or not these changes have addressed the most important characteristics of the air pollution mixture.

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CONTRIBUTORS

In Spring 2011, the Health Effects Institute appointed an expert panel to review and critique the scientific literature on the ultrafine particles — their sources, the role of automobile emissions, and their potential health effects at ambient levels of exposure. The panel consisted of scientists from a variety of disciplines and was chaired by Mark Frampton, a professor of medicine and environmental medicine at the University of Rochester Medical School. HEI is indebted to the panel for its expertise, cooperation, and enthusiasm. The panel also received support from a team of HEI staff, under the leadership of Katherine Walker, Senior Scientist. A draft of the resulting report was submitted for outside peer review; the help of the peer reviewers in improving the quality of this document is gratefully acknowledged.

HEI Review Panel on Ultrafine Particles

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