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

HEALTH EFFECTS INSTITUTE

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HEI Perspectives 3
Health Effects Institute
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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.

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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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.

The work of the HEI Review Panel on Ultrafine Particles was supported with funding from the United States Environmental Protection Agency (Assistance Award CR–83234701) and motor vehicle manufacturers. Support for the preparation and publication of this document was provided by the Federal Highway Administration (Grant DTFH61-09-G-00010). This report has not been subjected to peer or administrative review by any of the sponsors and may not necessarily reflect their views, and no official endorsement should be inferred.

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 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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U.S. National Research Council. 1998. Research Priorities for Airborne Particulate Matter: I. Immediate Priorities and a Long-Range Research Portfolio. National Academy Press, Washington, D.C.

Understanding the Health Effects of Ambient Ultrafine Particles

HEI Review Panel on Ultrafine Particles

CHAPTER 1. Introduction

The history of air pollution research and management has been characterized by efforts to identify the key pollutants responsible first for the major air pollution episodes that plagued the industrializing countries in the early part of the 20th century, and later, for the more subtle geographic variations in air pollution levels and health effects. Terms like smoke and haze have given way to more specific chemical entities — specific gaseous pollutants and solid particulate matter. In turn, the study of particulate matter (PM*) exposures, which began with crude measures of total suspended particles, evolved to focus on increasingly smaller particle size fractions that are more likely to be inhaled, beginning with PM ≤ 10 micrometers in aerodynamic diameter (PM_{10}), then ≤ 2.5 micrometers in aerodynamic diameter ($PM_{2.5}$), and recently on the complex mixture of constituents of which they are comprised. The fundamental motivation underlying these research efforts has been to identify those characteristics of air pollution that are most hazardous to human health and whose control would most likely lead to reductions in risks to public health. Interest in ultrafine particles (UFPs) — particles ≤ 100 nanometers in diameter — is very much a part of this history.

WHAT ARE UFPs AND WHY IS THERE CONCERN ABOUT THEM?

UFPs in ambient air make up the smallest size fraction in what is a continuum of particles with diameters ranging from a few nanometers to several micrometers (illustrated in Figure 1 for a typical roadway aerosol). By convention, UFPs have been defined as particles less than or equal to 100 nanometers in diameter (≤ 100 nm or ≤ 0.1 μm). UFP size fractions may also be characterized more generally in terms of the processes by which they are formed; *nucleation mode* particles (< 50 nm) and the larger *accumulation mode* particles (> 50 nm) (HEI 2010). UFPs technically are part of the larger size ranges that have been the primary subjects of air pollution studies (i.e., PM_{10} and $PM_{2.5}$). They contribute little to the mass of particles measured in these ranges, but are the dominant contributors to particle number.

Over the last 30 years, a large body of scientific literature has emerged that provides evidence of associations between short-term and long-term exposures to ambient PM_{10} and $PM_{2.5}$ and increased rates of mortality and hospitalization, primarily from cardiovascular and respiratory diseases. The most influential evidence first came from observational epidemiologic studies in the United States and around the world (e.g., Pope et al. 1992; Dockery et al. 1993; Anderson et al. 1997; Samet et al. 2000a,b; HEI 2003; Pope and Dockery 2006). The biological explanations for these findings were then, and continue to be, the subject of substantial research and debate.

Evidence from studies in laboratory animals had begun to accumulate by the early 1990s, which suggested that UFPs might penetrate more deeply into the lung and might be more toxic than larger particles (Oberdörster et al. 1990; Ferin et al. 1992; International Commission on Radiological Protection [ICRP] 1994). Of concern to air pollution scientists is that particles in the UFP size range account for the vast percentage of particle numbers in ambient air, even though they make up a small fraction of the $PM_{2.5}$ or PM_{10} mass (see Figure 1). A measured $PM_{2.5}$ mass concentration of 10 μg/m^3 for example, might contain as many as 2.4 million 20-nm particles/cm^3, but could also be represented by a single 2.5 μm particle (Oberdörster et al. 1995). Seaton and colleagues (1995) hypothesized that this *urban particulate cloud* of UFPs, could cause "alveolar inflammation,

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* A list of abbreviations and other terms appears at the end of this document.

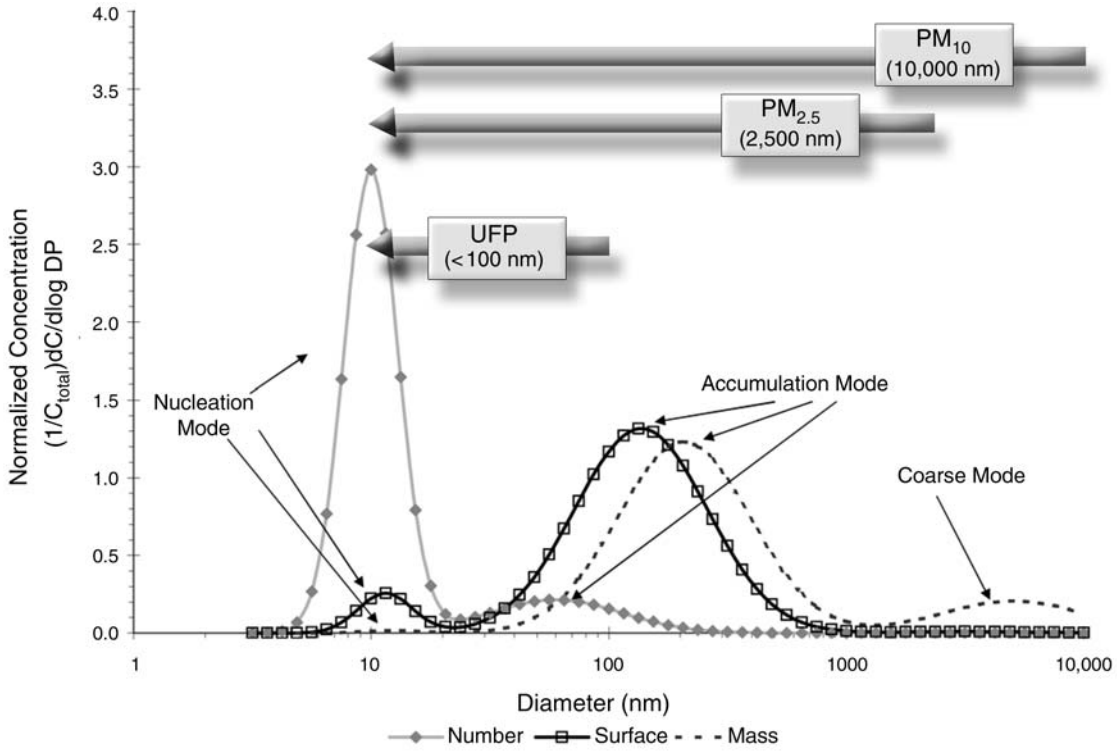

Figure 1. Normalized particle size distributions of typical roadway aerosol. Dp represents the particle diameter; $(1/C_{total})dC/dlog\ Dp$ represents the logarithmic particle-concentration-distribution function weighted by number, volume (surface), and mass. Here, C is the concentration (number, surface, or mass) in a particular size range and C_{total} is total concentration summed over all sizes. (Source: David Kittelson and Win Watts, reprinted from HEI 2010.)

with release of mediators capable, in susceptible individuals, of causing exacerbations of lung disease and of increasing blood coagulability, thus also explaining the observed increases in cardiovascular deaths associated with urban pollution episodes."

The high surface area per unit of mass of UFPs, a function of their vast numbers and small diameters, has also been hypothesized to be an important characteristic that might predict greater toxicity of particles in that size range. An early toxicologic study by Oberdörster and colleagues (1992), in which they instilled 20 nm titanium dioxide particles in the tracheas of rats, found that increased pulmonary toxicity was associated with the surface area of the particles. Other investigators have noted that surface area is a potentially important interface by which particles interact with biological systems and help to transport toxic metals or chemicals that may be adsorbed to the particles (Donaldson et al. 2005; Kreyling et al. 2006a; Maier et al. 2008).

Such early studies, coupled with later epidemiologic evidence that UFPs might be associated with adverse effects in humans similar to those observed for other particle size fractions (Pekkanen et al. 1997; Peters et al. 1997; Wichmann et al. 2000), motivated the U.S. National Research Council to identify UFPs as a research priority in their series of reports laying out a blueprint for a multifaceted research agenda on airborne PM (U.S. National Research Council 1998, 1999, 2001, 2004).

TIME FOR A BROAD PERSPECTIVE

In the decades since concerns were first raised about UFPs, these particles have remained an important research target at institutions around the world. At HEI, research on UFPs has been part of an ongoing effort to advance understanding of the associations between exposures to ambient PM and adverse effects on human health (see Appendix Table A.1 for a complete overview of HEI's research program involving UFPs, including published HEI reports with their related journal articles and ongoing HEI research). HEI's work has included some of the early research by Oberdörster and colleagues (2000) on the pulmonary effects of model UFP exposures in susceptible rats

and mice, as well as the first epidemiologic study to investigate and to observe an association of short-term daily exposure to UFPs with mortality (Wichmann et al. 2000). Several additional studies are still underway and include novel methods to improve real-time measurement and characterization of UFPs, modeling of personal exposures to UFPs from primary exhaust and secondary aerosols, and toxicologic and epidemiologic studies in settings with distinct variations in UFP concentrations.

Motor vehicles have often been cited as a key source of exposure to UFPs, and two recent HEI reviews have laid the initial groundwork on this issue. The HEI Special Report on traffic (HEI 2010) was an extensive review of the literature on traffic-related emissions, exposures, and associated health effects. As part of that report, UFPs were explored as one of several possible surrogate markers for exposure to traffic, but the evidence for supporting such a role for UFPs was found to be limited. HEI's Communication 16, a report of the HEI Special Committee on Emerging Technologies (HEI 2011), identified potential changes in UFP number emissions and composition that might be associated with future fuels and technologies.

Reflecting these ongoing concerns, UFPs continue to be considered by national and local air quality authorities in the United States and elsewhere in reviews of ambient air quality standards and other regulatory programs. The U.S. Environmental Protection Agency (U.S. EPA) assessed the evidence on UFPs as part of its most recent scientific review of the National Ambient Air Quality Standards (U.S. EPA 2009). While the agency judged the present health effects and air quality data to be insufficient to support an individual standard for UFPs, its scientific advisory panel, which reviews the U.S. EPA assessments, suggested that the role of UFPs continue to be evaluated and that future PM monitoring efforts be extended to the ultrafine range (Clean Air Scientific Advisory Committee [CASAC] 2010). In Europe, UFPs are one of several air pollutants being evaluated under the World Health Organization–led project known as REVIHAAP, which is designed to inform revisions of European Union policies on air quality in 2013.

Though not directly based on health considerations, the European Union has introduced particle number emissions standards for all diesel passenger and commercial vehicles, which are being introduced gradually over the period 2011–2013, and has required recently that they be extended to gasoline vehicles. These limits regulate the number of nonvolatile particles and effectively ensure that particle filters will be installed on both diesel and gasoline vehicles.

Future trends in the United States and other industrialized countries in the ambient levels of UFPs are somewhat hard to predict. On the one hand, the emissions, and therefore ambient levels, of UFPs will decrease under the force of regulations to reduce particle emissions from diesel vehicles; on the other hand, the growing use of gasoline direct injection technology — which raises fuel efficiency — is likely to increase UFP levels. The role that will be played by new fuels, such as ethanol and biodiesel blends and natural gas, remains largely ill-defined at this point.

Where are we now? With nearly two decades of research behind us, regulatory actions are underway that will influence emissions of UFPs. However, resolving questions about the specific role that ambient levels of UFPs may play in potential adverse effects on human populations remains a challenge. Given this context, HEI decided to form a special panel (listed on page ix) to review the scientific evidence available on UFPs. The expert panel held an initial meeting in July 2011 to lay the groundwork for the report and worked collaboratively thereafter with HEI staff to draft it. The draft was sent to 10 external peer reviewers and was revised extensively in response to their comments. The final result of this process is the current issue in the series of *HEI Perspectives*, in which we have sought to provide a broad overview of the scientific evidence regarding ambient UFPs, structured as responses to three questions:

1. **Ambient UFPs — sources, emissions, and exposures: To what extent do motor vehicles contribute?**

   Mobile sources are often cited as the leading source of human exposure to ambient UFPs. Chapter 2 explores the basis for this common statement by examining the many factors that affect the magnitude and potential for human exposures to ambient UFPs. We begin with a survey of the multiple sources of ambient UFPs and how they are measured. We then discuss in more 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 health studies of UFP exposures.

2. **Do UFPs affect health? What is the evidence from experimental studies in animals and humans?**

   Experimental studies play a critical role in the study of relationships between exposure and disease. They can be designed to characterize the patterns and mechanisms of particle deposition, clearance, and uptake that may be important to understanding the potential differential toxicity of particles. With carefully designed exposures and selected health endpoints in a controlled setting, these studies provide direct tests of hypotheses about the causal role of particular exposures. Chapter 3 focuses on the evidence from experimental studies

involving exposures to UFPs via the inhalation route, which is both more physiologically relevant and more directly comparable with the results of epidemiologic studies reviewed for the next question. We therefore excluded in vitro studies or studies in which particles have been directly instilled or deposited into the lungs or airways.

3. **Do UFPs affect human health at environmental concentrations? What is the evidence from epidemiologic studies?**

   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 answer whether UFPs affect human health at concentrations found in the environment. In Chapter 4, we evaluate the epidemiologic evidence: 1) for specific health endpoints, with an assessment of the consistency and coherence of observed associations, and 2) with respect to key study design and data issues, including how UFPs are measured, how exposures are assigned to subjects, and the extent to which potential confounding of the UFP effects by copollutants has been assessed.

Our responses to each of these questions have attempted to focus on literature most germane to the key issues. For example, our review of sources, emissions, and exposure has focused on studies that exemplify the major phenomena related to assessing ambient UFPs. In identifying experimental and epidemiologic studies for our assessment, we have focused on those involving combustion-related UFPs in order to make our assessment most relevant to conclusions about ambient UFPs, particularly those related to motor vehicle exhaust. We have therefore largely excluded the vast literature on engineered nanoparticles that has developed over the last decade, although we recognize that contributions from that literature may also provide insights. We also have placed particular emphasis on both experimental and epidemiologic studies of UFPs that include analysis of exposures to copollutant gases and larger particulate fractions because of their potential to provide insight to the role of UFPs themselves in any health effects observed.

Finally, Chapter 5 summarizes the main conclusions from Chapters 2–4 and attempts to draw some of their broader lessons. In particular, we discuss what the evidence to date allows us to conclude about the health effects associated with exposures to UFPs themselves, and how they differ from those of other particle size fractions and combustion-related copollutants. Possible directions for future studies that could enhance our understanding of emissions of, exposures to, and effects of UFPs are also provided.

CHAPTER 2. Ambient UFPs: Sources, Emissions, and Exposures. To What Extent do Motor Vehicles Contribute?

Many concerns about ambient UFPs have focused on their relationship to motor vehicle emissions. However, as a product of many combustion processes, as well as of secondary chemical and physical processes in the atmosphere, UFP concentrations measured in ambient air are affected by many factors over space and time. This chapter therefore seeks to provide greater perspective on the extent to which motor vehicle emissions may contribute to ambient concentrations of UFPs and ultimately to overall human exposure to ambient UFPs.

The chapter begins with a basic summary of the various methods by which UFPs are measured and characterized that provides a common terminology for the remaining chapters in which the methods are applied to health studies. It then presents a general overview of sources of ambient UFPs at regional and urban scales, offering some perspective on the relative contribution of motor vehicles and traffic. The next subsection provides some background on exhaust and non-exhaust emissions from current engine technology and briefly discusses the implications of changes in engine and fuel technologies for future emissions. The remainder of the chapter focuses on the potential for human exposure to ambient UFPs — in particular, on how concentrations and composition of UFPs vary over time and in different locations where human populations live, travel, and work. We conclude with a discussion of how such data might be used in animal and human studies to better assess the potential effects of UFPs on health.

HOW ARE UFPs MEASURED?

Several different sampling and analysis methods have been developed to analyze UFPs at different points in emission and in ambient air. Single-vehicle measurement offers the possibility of discerning engine, fuel, and aftertreatment effects on UFP emissions and assessing the effect of technology on emissions. Typically conducted in laboratory settings, these measurements may be made under controlled conditions, with set vehicle operating conditions, in a repeatable manner. Such measurements are dedicated to only a few vehicles, may involve stepwise in-laboratory dilution that differs from the faster and continuous atmospheric dilution, and may therefore result in sampling artifacts.

To avoid such limitations, investigators look to ambient sampling of vehicular aerosol to provide a more representative picture of the aerosol to which people in the

vicinity of roads may actually be exposed. Ambient aerosols reflect interactions of emitted particles with the environment (e.g., mixing with other particles and gases, photochemical reactions) that can occur over time and space. Disadvantages of this approach for characterizing the contributions of specific vehicles are that the ambient air may include aerosols contributed from different vehicles and vehicle types and typically reflects contributions from background pollutant concentrations and other local emission sources.

These challenges are not unique to the characterization of vehicular emissions and their contributions to ambient UFP concentrations. They affect efforts to study other sources as well. In general, all ambient measurements reflect the product of dynamic atmospheric and chemical processes that are likely to differ over time and geography.

However, one of the factors that has sometimes complicated comparison of data on UFP emissions, concentrations, exposures — and ultimately health effects — has been the many technologies and metrics (mass, composition, surface area, and particle number counts) that have been used to measure and describe them. To support discussions in this and later chapters, the following section describes the various methods by which UFPs are currently characterized; a simple summary of the terminology and the particle size ranges typically measured by the methods discussed is provided in Table 1.

Measurement of Ultrafine Particle Mass

While the measurement of the ambient concentrations of larger particle size fractions (i.e., $PM_{2.5}$ and PM_{10}) is typically based on the total mass per unit volume of air, or mass concentration, several factors make such measurements problematic for UFPs defined as those with diameters less than 100 nm ($PM_{0.1}$). First, direct measurements of UFP mass are challenging because the mass concentration of particles in the UFP range is very low. Ambient $PM_{0.1}$ concentrations are typically less than 1 $\mu g/m^3$, and commercial balances usually have practical detection limits of ± 1–5 µg for collection media (for example, filters) that weigh a few milligrams. These collection media can sustain only low flow rates (< 100 liters/min), so long collection times are required for sufficient mass to be collected for measurement. These sampling requirements in turn can influence another factor that can significantly affect sensitivity of mass measurements methods for these small size ranges — gas-to-particle artifacts. That is, chemical compounds in the gaseous phase may adsorb on particles to produce a positive artifact or, vice versa, desorb from the particle to produce a negative artifact. Although such processes generally occur in atmospheric conditions as well, the prolonged exposure of the PM to the air flow through the instrument may exacerbate these effects during sampling.

In practice, particle mass concentrations have been more typically estimated for UFPs in larger size fractions known as *quasi-ultrafines*; that is, UFPs < 0.180 µm ($PM_{0.18}$) or < 0.250 µm ($PM_{0.25}$) in diameter. Measures of quasi-ultrafine particle mass have been most commonly obtained with a class of instruments known as cascade impactors (see Table 1). In these instruments, particles are sorted and collected on a series of impactor surfaces, each corresponding to a successively smaller aerodynamic diameter cut-point. After collection on the cascade impactor stages, the mass for the fractions of interest is measured by gravimetric analysis. Or, in the case of the electrical low pressure impactor (ELPI) the particles are precharged and then the resultant current is measured on the impaction stages corresponding to various particle size ranges.

Multiple stages of cascade impaction are necessary for accurate UFP mass measurements, in part to remove larger particles from collection on UFP impaction stages. However, larger particles do sometimes bounce or otherwise pass through, and the results can be significantly altered by the accidental inclusion of a few larger size fraction particles with masses that are orders of magnitude greater than those of the UFPs. All of these factors have tended to favor forms of detection other than direct gravimetric analysis.

Reconstructed Particle Mass ($PM_{0.1}$)

As an alternative to direct UFP mass measurements, the concentration of individual chemical components can be measured in the $PM_{0.1}$ size range and combined to effectively reconstruct the total $PM_{0.1}$ mass. Detection limits for the dominant chemical components of $PM_{0.1}$ are usually much better than gravimetric detection limits for UFPs, making reconstructed $PM_{0.1}$ mass potentially more accurate. These measurements have the added advantage that they provide composition data that can also be used in $PM_{0.1}$ source-apportionment analyses.

The bulk of $PM_{0.1}$ mass is typically composed of carbonaceous material with smaller contributions from inorganic ions, reflecting the dominant combustion sources for these particles. The carbonaceous material can be broadly defined as compounds containing elemental carbon (EC) and organic carbon (OC). The EC and OC categories can be further separated into individual compounds, which can be especially useful for $PM_{0.1}$ source-apportionment studies. Due to the large fraction of carbonaceous compounds in

Table 1. Overview of Ultrafine Particle Measurement Methods[a]

Metric (units)	Abbreviation	Particle Size Ranges	Time Resolution	Method	Selected Instruments
Size-distributed particle mass concentration ($\mu g/m^3$)	PM_{x-y}	10 nm–18 µm Various cut-points: < 56 nm < 100 nm < 180 nm < 250 nm < 2.5 µm < 10 µm	Integrated (hr)	Cascade impaction	Cascade Impactors: MOUDI Nano-MOUDI Sioutas
Size-distributed number concentration ($particles/cm^3$)	PM_{x-y}	7 nm–10 µm Various stages	Integrated (hr)	Electrical low pressure impaction	ELPI
Number concentration ($particles/cm^3$)	Total NC	2.5 nm– 1000 nm (range can vary)	1 sec	CPC	Many models
Size distributed number concentration ($particles/cm^3$)	NC_{x-y}	Various ranges: 3–30 nm 30–300 nm 300–800 nm 2 nm–1 µm	1 min	DMA	SMPS
	NC_{x-y}	5.6–560 nm	1 sec	DMA	FMPS, ELPI
Size distribution (dN/dlogDp)		5.6–560 nm	10 samples/sec	DMA	EEPS
Particle size, number and mass		5 nm–2.5 µm	10 Hz data, 200 ms T10-90% response	Electrical mobility measurement	DMS500
Surface area ($\mu m^2/cm^3$)	SA_{x-y}	10 nm– 1000 nm	1 sec	Diffusion charging and electrometer	Nanoparticle Surface Area Monitor, DiSCmini, AeroTrak
		20 nm– 100 nm		Ionization and attachment of lead (Pb)	Epiphaniometer
		2.5 nm– 1000 nm (from SMPS)	1 min (from SMPS)	Derived from size counts assuming spherical particles, uniform density	SMPS
Composition		Various cut-points (see above)	Integrated (hr)	Cascade impaction, extraction, mass spectrometry	Cascade Impactors (see above)
		40 nm–1 µm	1–10 sec	Mass spectrometry	Aerodyne AMS
		30–300 nm	< 1 sec	Aerosol time of flight mass spectrometry	TSI 3800-030
		10–30 nm	< 1 sec	Aerosol time of flight mass spectrometry	NAMS

[a] AMS = aerosol mass spectrometer; EEPS = engine exhaust particle sizer; ELPI = electrical low pressure impactor; FMPS = fast mobility particle sizer; CPC = condensation particle counter; MOUDI = micro-orifice uniform deposit impactor; NAMS = nanoaerosol mass spectrometer; SMPS = scanning mobility particle sizer.

UFPs, efforts to reconstruct particle mass have focused more on using trace carbonaceous compounds to reconstruct total OC or EC in the particles (Kleeman et al. 2009). While larger dust particles may be mistakenly collected on UFP impaction stages, these tend to be made up primarily of crustal material, such as aluminum and silica.

The measurement of chemical composition is more costly and cumbersome than that of mass and is not currently suited to routine monitoring. However, information about chemical composition may be valuable when testing health effects hypotheses related to specific UFP components or sources.

Time-Resolved Measurements of UFP Chemical Composition

With the previous methods, the chemical composition of UFPs or quasi-UFPs is measured by collecting particles on substrates over some period. More recently, aerosol mass spectrometers and aerosol time-of-flight mass spectrometers have been developed that can measure the chemical composition signature of individual ambient UFPs (or groups of particles) over very short periods, seconds to minutes, for example (Bein et al. 2005; Toner et al. 2008; Klems et al. 2011). With these methods, the sampled particles are first broken down into their component major ions (laser ablation/ionization), which are then analyzed by mass spectrometer. The qualitative spectra produced by each particle can be grouped with similar spectra and compared to source libraries to identify probable emissions sources (Toner et al. 2008). These methods enable highly time-resolved source-apportionment studies of UFP number concentrations (UFP NC). As part of an HEI-funded project, Klems and colleagues (2011) have been developing a nanoaerosol mass spectrometer to measure the composition of individual particles in the 18–24 nm size range and have deployed it to assess the contribution of particular motor vehicles to ambient UFP number and mass concentrations at a major intersection in Delaware, Maryland. However, such methods are still undergoing development and have not been widely applied.

Surface Area Concentration

Given hypotheses about the biological relevance of the high surface area to mass ratio for UFPs, scientists have been particularly interested in measures of surface area to characterize UFP concentrations for use in health studies. As with determining particle size, however, defining a surface area that best describes biological interactions has not been straightforward. Most often, surface area is estimated from particle number and size distribution data and then making assumptions about particle shape, density, and other factors. Instruments have been developed to measure UFP surface area directly. The epiphaniometer estimates the Fuchs surface area as a function of radioactive decay from ^{211}Pb atoms attached to the measured particles (Gäggeler et al. 1989). Other surface area measurements entail exposing the UFPs to an electrical charge and measuring the resultant current (DiSCmini; Nanoparticle Surface Area Monitor; AeroTrak). Whether calculated or direct measurements characterize the surface area concentration of UFPs in ways that are biologically relevant has not yet been thoroughly studied.

Number Concentration

Perhaps the most straightforward measurement of UFP concentration is to count the total number of particles per unit volume of air, typically referred to as particle number concentration (NC) or for this document total NC. Given the relative ease and reliability with which they can be measured, total NC data are far more common than measures of particle mass, composition, or surface area. NC is also often assumed to be a reasonable proxy for surface area, as NC is assumed to be dominated by smaller particles and basic geometry dictates that, for a given mass of particles, surface area increases rapidly with decreasing particle diameter.

Total NC is generally measured continuously by condensation particle counters (CPC) in which particles previously enlarged by condensation of vapor on the particle surface are counted when they pass through a laser beam. Depending on the instrument, this method can count particles as small as 3 nm in diameter and typically includes particles up to 1000 nm or more in diameter. Although total NC measured this way is not strictly delimited by the 100 nm size definition for UFPs, it is often assumed to be dominated by particles in the UFP range (refer to Figure 1).

These instruments are very versatile and can provide number concentrations for discrete size ranges within the full distribution when used in combination with particle sizers such as differential mobility analyzers (DMA) which separate particles by size before they undergo condensation. The scanning mobility particle sizer (SMPS), for example, is an instrument consisting of both a DMA and a CPC. Due to cost and ease of use considerations, measurement networks have generally favored deployment of particle counters alone, although the use of size-differentiated particle counters is increasing. For this document, we have attempted to distinguish number concentrations for specific size ranges, when available, from total NC, rather than referring to all as UFPs.

Despite the appeal of these instruments, it is worth noting that number counts obtained by the different methods have potential limitations as indicators of UFP concentrations that should be taken into account when

interpreting and comparing results of different studies (Morawska et al. 2008). Although total NC has frequently been assumed to be synonymous with UFPs < 100 nm, particle size distributions in other environments are likely to differ from the idealized example for roadside aerosols shown in Figure 1. As indicated in Table 1, particle counters have different lower size limits, and unless specifically limited to 100 nm or another upper limit, number concentrations can have different meanings. Indeed, in a review of 52 studies, Morawska and colleagues (2008) compared total NC measurements obtained using CPCs with those obtained using methods that provide number counts for discrete particle size ranges (i.e., either differential mobility particle sizers [DMPS] or SMPS) for similar environments and estimated that mean and median number concentrations measured by CPC were significantly higher than those measured using DMPS or SMPS. Estimates of, or assumptions about relative surface area concentration, could also be affected. The implications of such differences for health studies have not been evaluated.

Summary of UFP Measurements

Numerous methods have been developed to measure the ambient concentrations and composition of UFPs. The various sampling and analysis techniques offer possibilities to analyze ambient particles in different ways, each with its own advantages and disadvantages. Given their simplicity and potential biological relevance, measurements of total NC have been the most common method used to measure UFPs, although as interest grows in the health relevance of particular size fractions, the use of methods that provide size-specific count data is increasing.

Since studies often report measurements or exposures for "ultrafines" or UFPs regardless of the specific measurement and sampling techniques that have been used, care should be taken when comparing, synthesizing, and interpreting results across studies. Emission factors and characteristics for UFPs should always be given with reference to the sampling conditions and procedure utilized. Otherwise, inconsistent findings in concentrations, size distributions and chemical composition are likely to exist and can complicate comparison of results.

SOURCES OF AMBIENT UFPs

Ambient UFPs have numerous sources. Most are related to combustion processes that include the burning of wood and other forms of biomass, and the combustion of fossil fuels for transportation, home heating, and cooking. UFPs may be emitted directly or may be formed secondarily through chemical reactions or particle–gas interactions in the atmosphere. This section focuses on primary emissions and briefly mentions the secondary formation of aerosol by a number of dynamic processes that occur in the seconds, minutes, hours, and days after an emission occurs.

Emissions Inventories

Emissions inventories, estimated from pollutant emissions factors for individual source categories, have long been used in air pollution studies to provide a regional perspective on the relative contribution of different sources to overall emissions of pollutants. However, few emissions inventories have been created for UFPs. Three are summarized in this section: one in California, one in the United Kingdom, and one in continental Europe. Though constructed using different approaches, they each point to a similar set of source categories, but the relative importance of particular sources has varied by location and time.

The one emissions inventory identified in the United States was conducted for California's South Coast Air Basin using $PM_{0.1}$ mass emissions data from 1996 (Figure 2); it estimated that on-road vehicles and other mobile sources (mostly off-road diesel) accounted for about 53% of UFP emissions (Cass et al. 2000). The emissions inventory from the United Kingdom is based on UFP mass emissions data for 1970 to 2007 from that country's National Atmospheric

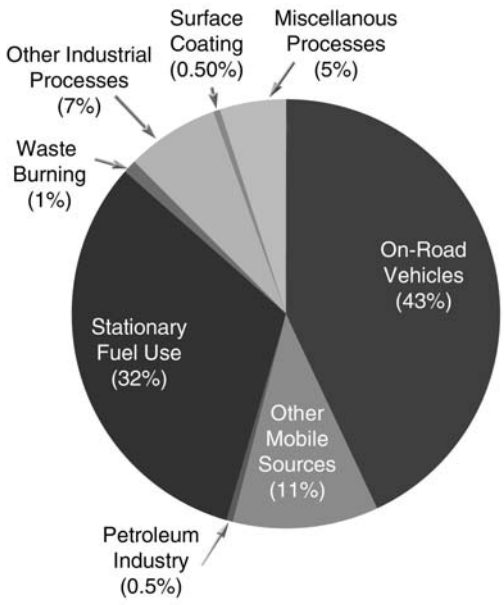

Figure 2. Source contributions to UFP emissions in California's south coast air basin (1996) that surrounds Los Angeles. Total $PM_{0.1}$ emissions were 13.25 metric tons per day. (Adapted from Cass et al. 2000, Figure 3a, with permission from the Royal Society.)

Emissions Inventory and is illustrated in Figure 3 (Kuhlbusch and Asbach 2011). It shows an overall decline in the total anthropogenic emissions of UFP mass over time, but shows traffic accounting for about 40% of total emissions in 2007, followed by industrial sources at 30%. The third emissions inventory, illustrated in Figure 4, is based on particle number emissions factors (for particles < 300 nm) for Europe in 2005 (Denier van der Gon et al. 2010; Kulmala et al. 2011). It suggests that road and nonroad transport together accounted for 51% of particle number emissions, followed by residential and commercial heating (21%), and various industrial processes (16%) accounting for most of the remainder (Denier van der Gon et al. 2010).

Although these inventories suggest similar source contributions, limitations of these inventories are that they are typically region specific, not verified with field measurements, and need to be updated over time as changes in emissions occur.

Source Apportionment

A second category of methods, source apportionment, has been used to estimate more directly the contribution of different sources to ambient UFP concentrations. These methods rely primarily on different statistical models (for example, chemical mass balance, principal components, and factor analysis) to infer the contribution of different sources from the chemical composition of particles measured at a given location.

Several source-apportionment studies of $PM_{0.1}$ mass alongside larger size fractions ($PM_{0.18}$) have been conducted at an urban location downwind of Los Angeles and in urban and rural locations of central California (Kleeman et al. 2009; Ham and Kleeman 2011), in the vicinity of major ports (Minguillon et al. 2008), and adjacent to roadsides (Riddle et al. 2008).

Such studies have traced $PM_{0.1}$ to a variety of sources including diesel and gasoline engines, residential wood burning, and cooking from fast food restaurants, among others (Martin et al. 2009; Ham and Kleeman 2011). Data from the same and related studies have also shown that the chemical signature of traffic sources can be estimated for the $PM_{0.1}$ size fraction several meters from major freeways (Kleeman et al. 2008a, 2009; Riddle et al. 2008) and that the relative contribution of different engine types and sources may vary with distance from roadways, by season, by time of day and by location (Kleeman et al. 2008a; Ham and Kleeman 2011). Figure 5 illustrates such variations by juxtaposing results of source-apportionment analyses based on the OC content of $PM_{0.1}$ from those studies. The chemical signature of the organic material in the $PM_{0.1}$ size fraction is altered by atmospheric chemical reactions as these particles age for several days in the atmosphere, making it difficult to link these particles to their emissions

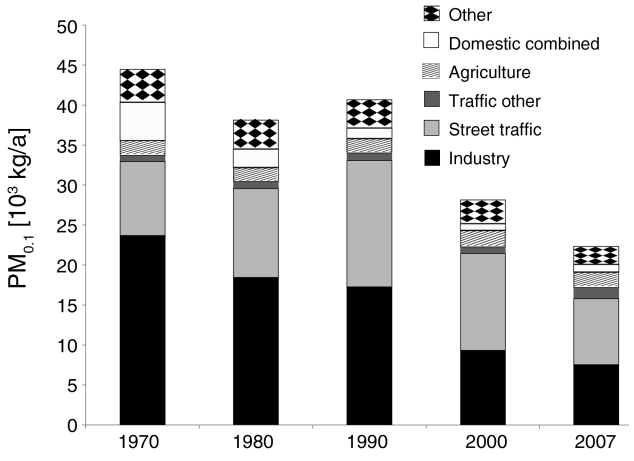

Figure 3. Emission inventory of $PM_{0.1}$ emissions in the United Kingdom from 1970 to 2007. Basic data from the National Atmospheric Emission Inventory (NAEI 2007). (Source: Kuhlbusch and Asbach 2011, reprinted with permission from John Wiley and Sons).

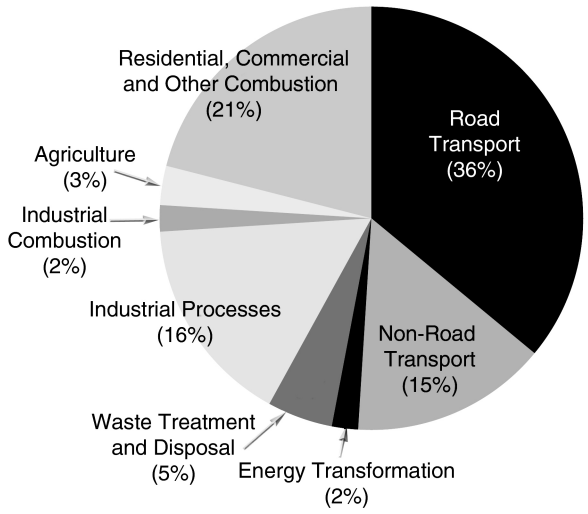

Figure 4. Source sector contributions in 2005 to European particle number emissions < 300 nm. (Total number of particles = 1.9×10^{27}). The estimated contribution from fossil fuel production was negligible. (Adapted from Denier van der Gon et al. 2010, using data provided by the author.)

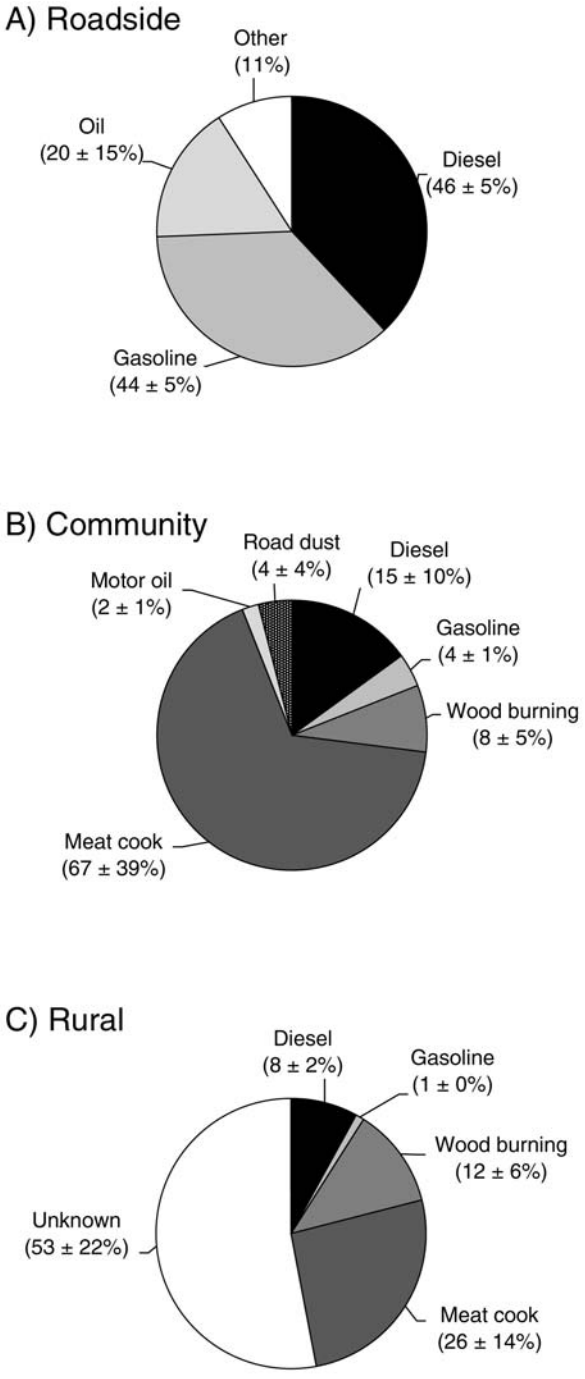

Figure 5. Predicted source contributions to $PM_{0.1}$ OC at varying distances from roadways. A: Roadside sampling site was 37 m downwind of Interstate 5 in San Diego, CA in summer; $PM_{0.1}$ OC concentration was 1.1 μg/m^3. **B:** Community sampling site was an urban site 400 m from a busy regional highway in Fresno, CA during the winter; $PM_{0.1}$ OC concentration was 0.07 μg/m^3. **C:** Rural sampling site was a rural site in Westside, CA in winter; $PM_{0.1}$ OC concentration was 0.09 μg/m^3. (Sources: Ham and Kleeman 2011, reprinted with permission from Elsevier; Riddle et al. 2008, reprinted with permission from the American Chemical Society.)

source using methods such as chemical mass balance that rely on the conserved chemical fingerprint of emissions.

Studies that analyze numerous measurements at a receptor site without the benefit of known emission chemistry profiles have generally yielded results that are consistent with the chemical mass analysis for UFPs. Kim and colleagues (2004) identified four dominant sources of UFPs in Seattle over a one-year study involving over 1000 measurements of particle size distributions. The lack of chemical fingerprint information made definite source identification impossible, but circumstantial evidence suggested contributions from traffic, wood burning, and secondary aerosol production from atmospheric chemical reactions.

Ogulei and colleagues (2006, 2007a,b) used a similar technique to identify primary $PM_{0.1}$ source contributions from traffic and industrial point sources in Baltimore, Maryland (2006); Buffalo, New York (2007b); and Rochester, New York (2007a), confirming that point sources can be important in regions downwind of industrial activities. In a further analysis of the Rochester data, Wang and colleagues (2011) measured a ~50% reduction in UFP concentrations when a local coal-fired power plant was converted to natural gas.

Two European studies have identified road traffic as a dominant source in Europe, using different methods to apportion sources. Pey and colleagues (2009) in Barcelona, Spain, used factor analysis and multilinear regression analysis to analyze $PM_{2.5}$ and particle number measurements (0.013 μm–0.800 μm). They attributed between 54% and 86% of UFP numbers in the 0.030–0.2 μm size range to road traffic. Lonati and colleagues (2011) used factor analysis and other methods to analyze the daily patterns of particle number size distributions in Milan, Italy; they concluded from their results that fresh traffic exhaust emissions were the primary source of UFPs in the city and were a strong contributor to their concentrations at urban background sites as well.

These studies have been important in extending source-apportionment methods to the UFP size fraction and comparing the source contributions to different particle size fractions. However, they also illustrate that the same sources contribute to multiple size fractions at the same locations, which can complicate exposure and health studies focused on UFPs.

Particle Number Counts by Location

A third, more general approach to illustrating the effect of traffic has been to report and compare the particle concentrations observed in different locations presumed to be differentially affected by traffic. Morawska and colleagues (2008) conducted a meta-analysis of 71 studies of NCs in multiple

geographic locations and showed that particle counts were progressively higher as the potential for traffic effects became greater. These findings are summarized in Figure 6 and show that mean NCs ranged from 2,600 particles/cm^3 in clean background areas to 10,760 particles/cm^3 in urban areas, to 48,180 particles/cm^3 at roadsides, and to 167,700 particles/cm^3 inside traffic tunnels where ventilation is relatively low. The relative contribution of other sources to the number concentration in urban areas cannot be assessed in these studies.

Summary of Ambient UFP Sources

Ambient UFPs have many sources, most related to combustion processes. They may be emitted directly or may also be formed from multiple precursors as part of secondary atmospheric processes. In urban areas, motor vehicles are often the leading source, particularly in proximity to roads. Source-apportionment studies indicate that other point sources may be important contributors to UFP concentrations at increasing distances from roads, and that the relative contribution may vary by geographic location, season, and time of day.

EMISSIONS OF UFPs FROM MOTOR VEHICLES

This section of the report seeks to provide an understanding of emissions of UFPs from the major classes of engine technologies, the characteristics of these particles, and how they may change over time as new technology is introduced.

In recent decades, attention has focused on the emissions associated with diesel engines. Figure 7 helps explain why. For the transport sector of the 2005 European particle number emissions inventory shown earlier in Figure 4, it shows a breakdown by engine type (Denier van der Gon et al. 2010). In almost every particle size category, diesel engines including both light-duty (passenger and light commercial vehicles) and heavy-duty (trucks, buses) accounted for a large portion of the total particle number emissions from the transport sector. Contributions to total emissions from other engine types and to a much lesser extent, from non-exhaust sources (tire and brake wear) are also projected.

However, the relative contribution of diesel engines to total and transport-related particle number emissions is likely to vary locally or regionally depending on the composition of the vehicle fleet. The work in southern California that was discussed in the previous section (Kleeman et al. 2008b; Ham and Kleeman 2011) illustrated how the source contributions to UFP concentrations can differ depending on the type of vehicles dominant on particular roads. On a regional scale, Keogh and colleagues (2009) modeled emissions contributions to PN emissions for urban southeast Queensland in Australia where they estimated that 93% of the vehicle kilometers traveled were accounted to light-duty, gasoline-powered vehicles and about 6% to

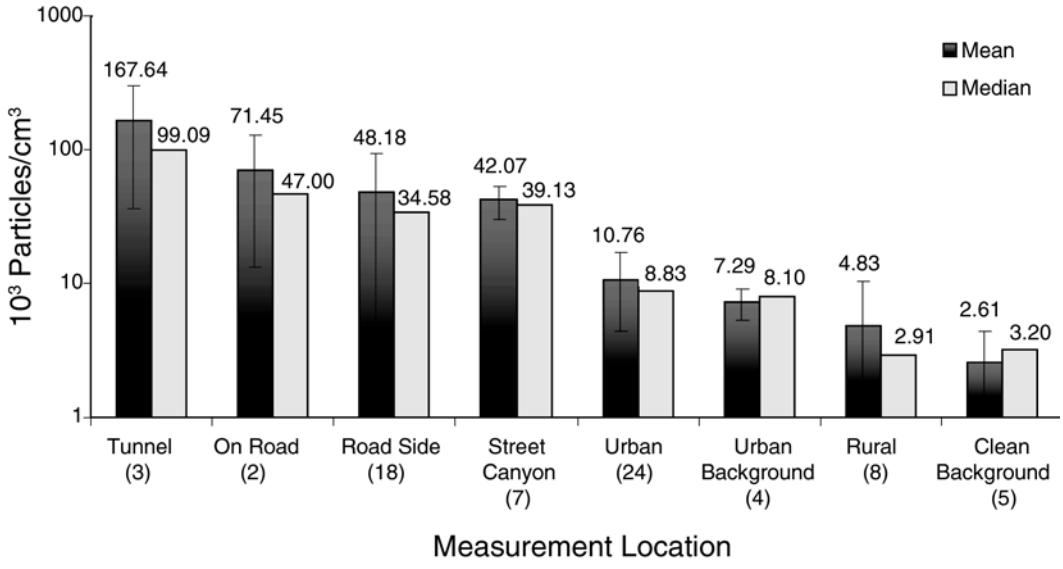

Figure 6. Mean and median particle number concentration (log scale) for different environments. The number of sites for each environment are in parentheses (e.g., 3 tunnel studies). (Source: Morawska et al. 2008, reprinted with permission from Elsevier.)

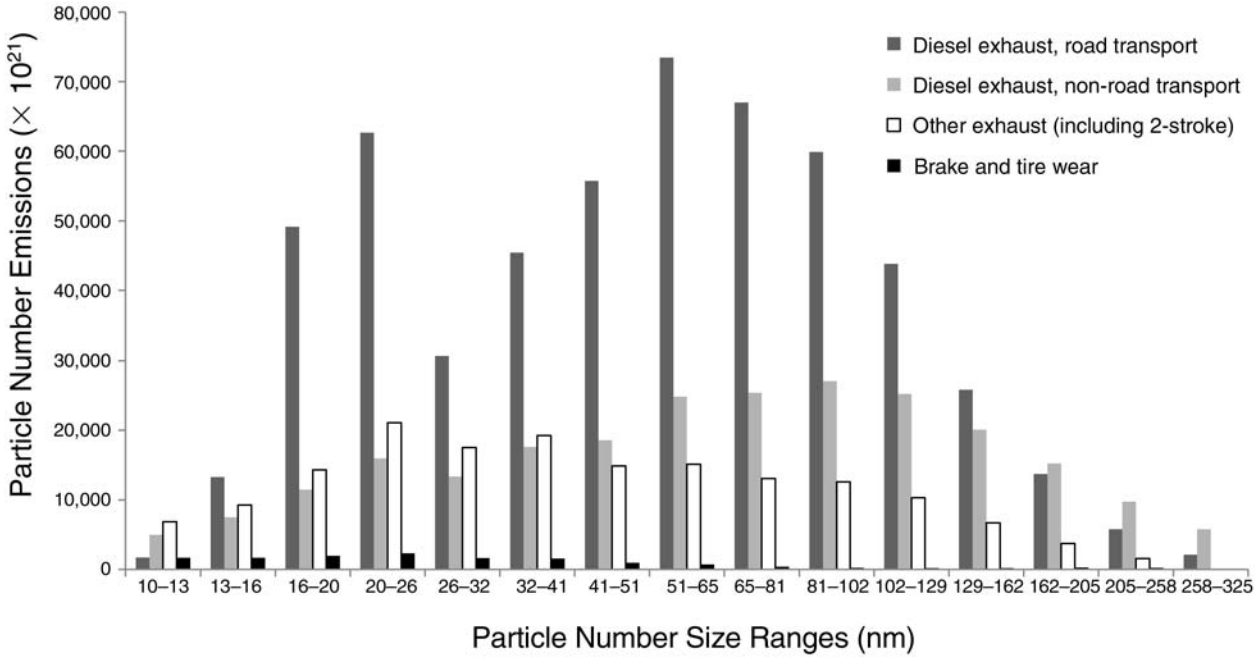

Figure 7. Estimated particle number emissions from road transport and non-road transport (railway, inland navigation, and mobile machinery) in Europe for 2005, excluding international shipping. The diesel exhaust emissions were based on the diesel fleet composition in 2005. (Adapted from Denier van der Gon et al. 2010.)

heavy-duty diesel vehicles. In that example, heavy-duty diesel engines still accounted for more than 50% of daily particle number emissions (3 to 1000 nm) but light-duty vehicles also contributed 45%. Particle number emissions from diesel and compressed natural gas (CNG) buses were comparatively much lower. Equivalent inventories of number emissions for the United States were not identified.

Generation and Characterization of UFPs in Engine Emissions

UFPs emitted from motor vehicles are primarily a product of the combustion process. They are formed in the engine during the combustion process itself as well as during the journey of the exhaust as it moves through the exhaust line and then through aftertreatment devices to the tailpipe from which it is released to the atmosphere. As the exhaust gradually cools during this journey, volatile and semivolatile materials such as organic components and ions may nucleate, thus forming new particles. This process produces UFPs in the few nanometer size range that may coagulate to form larger particles, may gradually grow in size as material condenses on their surface, or if composed solely of volatile species, may evaporate completely. However, particles formed from nucleation — sometimes called *nucleation mode* particles — are almost fully confined within the UFP size range (Kittelson 1998).

The formation and subsequent physical and chemical changes in UFPs prior to their release from the tailpipe is a function of engine characteristics and aftertreatment technology, fuel type, engine operating conditions (including state of maintenance), and ambient conditions. This section provides an overview of the typical number, size, and mass ranges of UFPs from compression-ignition (diesel-powered) and spark-ignition (gasoline-powered) vehicles, giving special emphasis to the formation characteristics of nucleation mode particles and the effects of aftertreatment technology such as diesel particle filters (DPFs) on particle numbers and composition. It also reflects on differences in emissions from light-duty and heavy-duty engines, on the effects of DPF regeneration, and finally on the implications of new fuel and technology specifications for future emissions.

Diesel Engines Particle emissions from diesel engines have been studied and characterized extensively; indeed, a large part of our understanding about the physicochemical and toxicologic properties of PM is based on studies that have used diesel emissions. Although several general conclusions can be reached about the nature of PM emissions

from earlier generations of diesel engines, diesel engine technology has undergone radical changes during the last decade. Improvements in engine design and operating conditions, a combination of low-sulfur diesel fuel, and the use of highly efficient aftertreatment systems have led to significantly reduced diesel PM emissions. New diesel engines currently being sold in the industrialized countries are contributing to an important and noteworthy shift in the composition of the diesel fleet in these regions. However, during this transition, many older technology engines will remain on the road both in industrialized countries and particularly in developing countries where the introduction of the newer technology has not yet occurred. Consequently we discuss emissions from old- and new-technology engines and also describe differences between their exhaust emissions.

Emissions from Old-Technology Diesel Engines Diesel ultrafine PM is one of the most well analyzed components of vehicular PM. David Kittelson (1998) first introduced the concept of a trimodal exhaust size distribution, illustrated in Figure 1. Results from that study are representative of emissions from the older heavy-duty diesel vehicles. In particular, it showed that a large number of particles in the size range below 50 nm may be formed by nucleation, especially from engines that produce a high concentration of volatile and semivolatile components. The concentration of nucleation mode particles measured in the on-road exhaust plume can reach $10^9/cm^3$ with a mean size around 10 nm (Giechaskiel et al. 2005; Kittelson et al. 2006). Such nucleation mode particles have since been observed by measurements on a number of different vehicles and sampling conditions; the many mechanisms proposed for the formation of such volatile particles have been summarized in a review by Seigneur (2009) of key studies reported in the period between 1998, when the Kittelson paper was published, and 2007.

The majority of accumulation mode particles (> 50 nm) also fall well within the UFP size range on the basis of number but not mass (see Figure 1); this distinction between size and mass distribution is particularly important to keep in mind. Particles in this mode consist of a nonvolatile agglomerate core on which volatile and semivolatile material adsorbs or condenses. The size distribution curve for typical accumulation mode particles from diesel engines without DPFs has a lognormal shape with a mean particle size of approximately 60 nm and a tail extending down to the 20–30 nm range. Peak concentrations on the order of 10^8 particles/cm^3 have been observed at the tailpipe or nearby on the road (Kittelson et al. 2006; Giechaskiel et al. 2009).

While nonvolatile particles have generally been associated with the accumulation mode, a growing body of evidence suggests that they may also appear in the nucleation mode. This phenomenon has primarily been observed during engine idling (Kittelson et al. 2006) and has been attributed to metallic ash formation, primarily from lubrication oil. More recently, the presence of a combustion-generated nonvolatile solid core in the size range below 10 nm has been recorded in emissions from heavy-duty diesel vehicles (Lahde et al. 2010) and light-duty diesel vehicles (De Filippo and Maricq 2008). There are indications from one study that such particles can be formed by spark-ignition combustion as well (Sgro et al. 2008). The exact origin of these particles, the conditions favoring their production and the frequency of appearance in vehicle exhaust are not yet identified. However, the concern is that these may act as condensation sites for the formation of UFPs before or while the exhaust is diluted in the ambient air.

Emissions from New-Technology Diesel Engines In view of health and other concerns about emissions of PM from diesel engines, the United States and other industrialized countries have mandated stringent regulations to control emissions. One of the first regulatory steps taken was to reduce the levels of sulfur in diesel fuel from about 2000 ppm to 500 ppm in 1995, with further reduction to 15 parts per million (ppm) in the United States by 2006; equivalent reductions were made in diesel fuels in Europe by 2010. These changes reduced the levels of particulate sulfate emitted. In combination with the low-sulfur diesel fuel, DPFs have now been introduced. DPFs are made from ceramic or other porous materials and are generally coated with metallic catalysts; in some cases a diesel oxidation catalyst device is also positioned upstream of the DPF to enhance effectiveness (HEI 2011). DPFs have been a pivotal factor in emission reductions; they have been shown to be effective in practically eliminating particle emissions across the size spectrum, including the UFPs (Coordinating Research Council 2009; Tzamkiozis et al. 2010; Khalek et al. 2011). However, because the DPF technology is relatively new, and also because the numbers and mass of particles emitted are extremely low, relatively few studies have been done to characterize the PM emissions in detail.

Although DPFs have been highly effective at reducing particulate emissions, two issues related to the use of DPFs deserve further attention. First, several studies now suggest that under certain conditions, DPFs contribute to the formation of nucleation mode UFPs with a high fraction of sulfate (Tzamkiozis et al. 2010; Herner et al. 2011). In a detailed study, Herner and colleagues (2011) report that the emission of nucleation mode particles depends on the

condition and configuration of the aftertreatment system, engine operating conditions (particularly exhaust temperature in the aftertreatment system), and the sulfur content of fuel and lubrication oil (see also Hesterberg et al. 2011).

Secondly, high-efficiency particle filters can become loaded with soot particles, which must be removed to prevent plugging. Removal is done by oxidizing the collected soot particles in place in a process called regeneration. During regeneration, transient high UFP emissions have been observed (Bergmann et al. 2009; Khalek et al. 2009, 2011). For example, in the testing of new-technology diesel engines described above, most of the UFP emissions were confined to the regeneration phase which generally lasted 30 to 45 minutes (Khalek et al. 2011). Still, the use of modern aftertreatment technologies represents a very important advance in reducing diesel emissions and are expected to improve air quality.

Comparison of Emissions from Old-Technology vs. New-Technology Diesel Engines As mentioned above, the PM emissions from old- and new-technology diesel engines are different in several respects; these differences are discussed below and summarized in Figure 8.

Mass: The PM mass emitted from the new-technology engines is far lower than that from the old engines. For example, comparing the results of two series of tests, with 2004 engines (Coordinating Research Council 2007) and 2007 new-technology engines (Khalek et al. 2011), the mass of emitted total PM is reduced by 89% (Coordinating Research Council 2009). Other authors have reported similar reductions.

Number emissions: Based on a comparison of two series of tests reported in Coordinating Research Council 2007 and 2009, the number of particles emitted by the new-technology (2007 model year) vs. the old-technology (2004) engines is lower by more than 100-fold; during regeneration events, when most of the PM is emitted, the particle numbers are still 10-fold lower as compared to the 2004 engine tests.

Chemical Composition: New-technology diesel engines also have a significant effect on the chemical composition of diesel emissions (Maricq 2007; Biswas et al. 2009; Coordinating Research Council 2009, Hesterberg et al. 2011). PM from old-technology engines contains significant amounts of both OC and EC (with the latter being in excess), along with sulfate, metals and other ions. DPFs reduce the mass of EC present in solid particles, reduce volatile components that contribute to OC, and render the proportion of OC greater than EC. Also, the relative proportion of sulfate in the particles is now higher than it is in old-technology engine emissions. DPFs also effectively (> 95%) reduce the metal content of PM exhaust over typical driving cycles (Hu et al. 2009; Cheung et al. 2010).

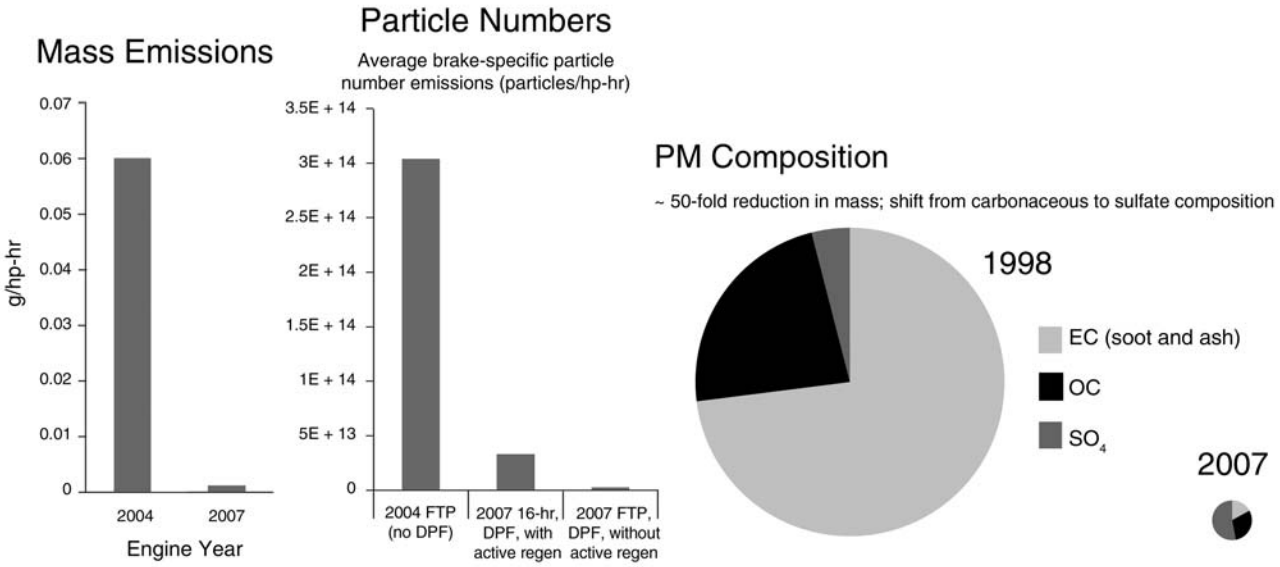

Figure 8. Comparison of the mass, numbers, and composition of emissions from old-technology and new-technology diesel engines. (Sources: 1998 data from Khalek, Personal Communication 2012; 2007 and 2009 data from Coordinating Research Council 2007, 2009.)

To meet the stringent 2010 nitrogen oxides (NO_x) standards established by the EPA and similar rules in Europe, manufacturers of diesel vehicles have developed methods for selective catalytic reduction (SCR) of NO_x compounds. Some SCRs use vanadium (as V_2O_5) in the catalytic formulation. However Hu and colleagues (2009) have shown that vanadium-containing SCR systems, may release vanadium in the UFP size range if the temperature of the exhaust is too high. In the United States, vanadium-based SCR are used for agricultural and other nonroad applications, but on-road vehicles use copper-zeolite catalyst, which is stable at higher temperatures. In Europe for heavy-duty applications (and increasingly in developing countries), vanadium-based catalysts are more common.

Spark-Ignition Engines Gasoline spark-ignition engines, provided that they are well maintained, produce only small amounts of PM under normal operating conditions. Recently, in response to the call for increased fuel efficiency, gasoline direct injection or direct injection spark ignition (DISI) technology is being widely adopted. While helping to boost fuel economy, however, DISI engines produce increased numbers of UFPs. Concern about the increased UFP emissions from DISI technology has led to the development of alternative fuel injector designs; the spray-guided, center mounted injector appears to be particularly promising in reducing particulate mass and number emissions.

Conventional Gasoline Engines The dominant method used to introduce fuel in the combustion chamber of gasoline engines has been port injection. Under normal operating conditions in modern gasoline engines, negligible numbers of UFPs are formed. Conditions do exist, some transient and some longer term, under which these engines may be significant contributors to UFP emissions. During start up under cold temperature conditions (cold starts), UFP emissions can increase, as can emissions of other gaseous pollutants. For example, Mathis and colleagues (2005) showed that gasoline particle number may reach diesel-like levels in tests at -7°C and -23°C. Such emissions are clearly of greater concern in colder climates where they may be important contributors to UFP concentrations under certain conditions.

Poor engine maintenance can also lead to increased emissions of UFPs. Light-duty gasoline vehicles with visible smoke emitted from their tail pipes due to engine malfunction (so-called *smokers*) may be significant contributors due to emissions from partial combustion of lubrication oil. Robert and colleagues (2007) estimated the UFPs emitted by smokers to be 10 mg/km compared with 0.05 mg/km for modern gasoline cars operating on mild driving cycles, and with 2 mg/km for cars operating on more aggressive driving cycles.

In gasoline PM, OC dominates the mass of UFPs, followed by EC with traces of ions, including calcium, ammonium, sulfate, and various metals (Geller et al. 2006; Robert et al. 2007). Typically, gasoline UFPs contain a higher fraction of heavy polycyclic aromatic hydrocarbons (PAHs) than diesel exhaust (DE) which may have implications for the differential toxicity of these particles (Geller et al. 2006; Cheung et al. 2010).

Gasoline Direct Injection Engines The direct injection of fuel into the cylinders of gasoline engines is increasingly being used because it improves fuel efficiency and performance. The gasoline DISI provides better control of the air-to-fuel ratio, especially while starting an engine and during warm up. Another important feature of the DISI is that it allows the use of a higher engine compression ratio, made possible because of cooling of the contents of the combustion cylinder as the direct-injected fuel spray evaporates. Because of the less complete mixing of fuel vapor and air, however, the particulate emissions of the engine increase, including the number of UFPs (HEI 2011).

Studies have shown the size distribution of particles emitted by DISI engines is similar to that emitted from non-DPF diesel engines (Harris and Maricq 2001), and the particle numbers emitted can sometimes be only 4–5 times lower than typical non-DPF diesel cars (Ntziachristos et al. 2004). The high particle number of DISI vehicles has raised questions about the need to install particle filters in DISI vehicles; it has also led to an intense interest in fine tuning the injection–combustion control system that can reduce the UFP emissions problem. The development of spray-guided fuel injectors shows a great deal of promise in this regard.

Other Types of Combustion Engines Small gasoline engines, in particular two-stroke engines installed in mopeds and scooters, are a significant source of particle emissions. In such engines, rich combustion, early scavenging of combustion products, in-cylinder injection of lubricant oil, and poor maintenance lead to elevated hydrocarbon emissions which may condense to form UFPs. UFP emissions from such engines have been shown to exceed typical diesel engines by more than one order of magnitude (Ntziachristos et al. 2005). The air quality implications of such high UFP emissions are of particular importance in developing countries where a significant population of such vehicles is still in operation (Begum et al. 2006).

Off-road machinery, such as construction equipment, diesel power generators (especially those used in developing countries), lawn mowers, and marine engines, has been a significant source of pollution in certain locations. Among the industrialized countries, regulations are gradually being introduced to control such sources. However,

the smaller of such sources — such as lawn mowers and other gardening equipment used by large numbers of consumers — are still not well controlled and may be a source of PM exposure. The situation in developing countries also deserves much attention.

Non-Exhaust Sources

Vehicles also generate PM through mechanical processes, namely wear on tires and brakes, abrasion of road surfaces, and resuspension of road dust. The particle number emissions inventory, displayed in Figure 7, projects a contribution to total 2005 UFP emissions from tire and brake wear (but not including road-surface wear or resuspension) that is substantially smaller than that from exhaust, on the order of a few percent at most depending on particle size (Denier van der Gon et al. 2010).

A laboratory study of debris released during braking events found that mechanical processes generally resulted in a distribution of particles with mean diameters in the range of a few micrometers but with tails extending to the UFP range; the number and size distribution varied with brake materials and other factors (Sanders et al. 2003). In addition to mechanically-generated particles, there has been some evidence of thermal particle formation due to the heat produced in cornering and braking (Dahl et al. 2006; Kukutschova et al. 2011). These particles have not been well studied to date.

Vehicles contribute to an increase in ambient PM through abrasion of road surfaces and resuspension of road dust in the vehicle wake. However, the particles that accumulate on the road are in the micrometer size-range or larger. Smaller particles are not likely to settle on the road surface, but they are scavenged out of the atmosphere by precipitation or by photochemical reactions. Hence, the contribution of particle resuspension to UFP concentrations is likely to be negligible, although measurements to confirm this assumption are necessary.

Finally, in old engines, crankcase emissions have also been a source of UFPs (Rim et al. 2008; Tatli and Clark 2009). These should have been effectively addressed with the post-2007 emission standards that have implicitly called for closed-type crankcase breathing systems.

Potential Effects of Other New Fuels and Technologies

The development of new fuels and technologies is progressing rapidly in response to various pressures for alternative fuels, the need for greater fuel economy, and efforts to reduce air pollution. Such changes in fuels and technologies are likely to affect both overall emissions and the relative contributions from different vehicle classes. However, these effects are not yet well characterized.

Buses Powered by CNG UFP emissions from CNG buses have been studied in some detail in an effort to understand whether CNG buses can be a successful alternative to diesel buses with advanced aftertreatment systems. Particle number emissions of CNG buses are typically one order of magnitude lower than those of diesel buses without DPFs at low loads, but the CNG bus emissions can reach diesel-like concentrations during acceleration and at high load (e.g., Nylund et al. 2004; Jayaratne et al. 2009, 2010). In all cases, particle mass is a fraction of total PM emissions, implying that these particles are in the UFP size range. It appears that emissions largely result from lubricating oil consumption and are affected by catalyst location and the engine type (lean-burn versus stoichiometric). It has also been shown that, similar to spark-ignition engines, OC dominates the mass of particles from CNG buses; EC and inorganic species make up some 30% of the total mass (Okamoto et al. 2006).

Biodiesel Use of biodiesel is seen as one part of a multipronged approach to reducing greenhouse gas emissions from transport, but the implications for UFP emissions deserve some attention. Biodiesel is a synthetic fuel derived from plant or animal products and blended with fossil diesel fuel at low percentages (10% to 20% by volume, sometimes lower in Europe). These blends generally produce lower emissions of total PM mass. Under certain conditions, however, and even in low blending ratios, biodiesel may enhance the formation of nucleation mode particles (Heikkila et al. 2009; Fontaras et al. 2010; Chuepeng et al. 2011). The UFPs produced contain reduced amounts of EC as a result of decreased soot formation and enhanced in-cylinder oxidation of any particles formed (Jung et al. 2006; Hoekman et al. 2009).

Ethanol Gasoline containing 10% ethanol is widely sold in the United States, and the use of ethanol is poised to increase in the coming years with higher blend levels. The blending of ethanol in fuel can lead to higher volatility of the blended fuel. To compensate for this, lower volatility base gasoline is usually used, which could contribute to less homogeneous mixing of fuel and air in the combustion chamber and poor evaporation, and in turn to higher UFP emissions. Data concerning the effect of ethanol on UFP emissions is limited; however, no substantial variations of the already low UFP emissions of gasoline-powered vehicles appear likely (Lee et al. 2009). After extensive modeling, the U.S. EPA (2010) concluded that the use of ethanol blends will lead to only minor changes in annual or daily PM_{10} or $PM_{2.5}$ concentrations; the effects on UFPs were not specifically evaluated. Emissions of PM may also arise from poor maintenance of vehicles (e.g., erroneous

recognition of the petroleum/ethanol blend ratio could lead to nonstoichiometric combustion with significant effects on releases of UFPs).

Electric Drive Technologies Hybrid electric vehicles, plug-in hybrid electric vehicles, battery electric vehicles, and fuel cell vehicles have started to be marketed in many countries during the last few years. With tailpipe emissions at least comparable to the cleanest available gasoline engines (in the case of hybrid electric vehicles and plug-in hybrid electric vehicles) to zero emissions (in the case of battery electric vehicles and fuel cell vehicles), the increasing employment of such vehicles in the market should eventually have a net beneficial effect on all traffic-related emissions, including those of UFPs.

Summary of Motor Vehicle UFP Emissions

UFPs from motor vehicles are emitted primarily in exhaust from internal combustion engines. Non-exhaust sources such as mechanical wear on tire and brakes, abrasion of road surfaces, and resuspension of road dust have begun to receive some attention, but their contributions to emissions of UFPs have not been extensively studied.

Diesel engine technology, in particular, has historically favored the formation of particles in the ultrafine range, so their emissions and the factors giving rise to them have been extensively characterized. Changes in the sulfur content of diesel fuels, optimization of engine design and operating conditions, and the use of modern aftertreatment technologies have led to substantial reductions in diesel engine UFP emissions as well as to significant changes in their chemical composition. However, emissions of UFPs during DPF regeneration events and under other engine operating conditions deserve further attention.

Well-maintained gasoline spark-ignition engines using conventional port injection technology produce little UFP or other PM emissions under normal operating conditions. Newer fuel-efficient gasoline engines using DISI technology have been found to release UFPs in similar size ranges as diesel engines, but at a lower rate of emissions. Optimization of engine design and operating conditions to reduce emissions are being pursued, and the need for DPFs is being considered.

These two engine technologies, while they currently dominate the automotive fleet and consequently receive the most focus, are not the only types of combustion engines that contribute to UFP emissions. Rapid changes are occurring in fuels and in technologies that are likely to affect overall emissions, the relative contributions from different vehicle classes, and the relative importance of non-exhaust sources. The collective impact of all these changes on either overall emissions or ambient concentrations has not been thoroughly explored and is likely to vary regionally depending on the rate and extent to which they are deployed in different parts of the world.

CHARACTERIZING HUMAN EXPOSURE TO AMBIENT UFPs

The characterization of the sources and emissions of UFPs is an important first step. However, understanding the potential implications of these emissions for human health requires characterization of potential human exposures — how the concentrations and composition of UFPs vary over time and in the different locations where people live, travel, and work. Such information helps inform the design of relevant exposures for use in experimental settings with animal and human subjects (Chapter 3). Epidemiologic study designs take advantage of these variations in ambient concentrations to explore their implications for human health (Chapter 4). In the case of PM_{10} and $PM_{2.5}$, such studies have played key roles in determining the numerical levels at which ambient standards are set.

Providing a comprehensive characterization of UFP concentrations is challenging because no networks of UFP monitors currently exist. Instead, studies often provide a snapshot of specific locales at particular points in time, often relying on different monitoring methods. They may, or may not, include measurements of other pollutants, including other particulate size fractions and gaseous copollutants, that may ultimately be needed to understand more specifically the role of UFPs and their sources on health. To augment measurement data, various efforts to model UFP concentrations are also under development.

This section of the document provides an overview of what these studies tell us about how ambient UFP concentrations vary over time and space, in particular in relation to traffic in urban areas. Like the majority of studies, this summary focuses variation in measures of NC with some data on differences in particle mass and composition.

Factors Affecting Concentrations and Composition of Ambient UFPs

Numerous processes influence the concentrations and composition of ambient UFPs over different spatial and temporal scales. At a very local scale, Figure 9 schematically illustrates the typical evolution of an exhaust aerosol packet immediately before and after it leaves the tailpipe of a diesel vehicle not equipped with DPFs. It describes the processes leading to changes in the size distribution and dilution ratio with increasing distance from the tailpipe until particles merge into the urban background.

Once emitted directly to the atmosphere or nucleated in the cooled exhaust from combustion sources such as motor vehicles, UFPs undergo coagulation and gas–particle exchange with the surrounding atmosphere (Zhang et al. 2004). Coagulation (particle collision and adherence) favors the transfer of the smallest UFPs to the larger size fractions, usually with diameters > 100 nm, over timescales of a few hours. This process can be an effective atmospheric removal mechanism for primary UFPs, which have very low settling velocities (Herner et al. 2006). Gas–particle exchange (condensation or evaporation) favors the growth or shrinkage of particles in the cooled combustion exhaust depending on the concentration of the surrounding gas-phase material over timescales of seconds to minutes (Zhang et al. 2004). As dilution with ambient air cools the exhaust, the gas-phase material initially becomes supersaturated, leading to nucleation and growth of semivolatile organic compounds. Continued dilution reduces the gas-phase concentration below the saturation level, causing the nucleated particles to evaporate completely or leaving the solid primary cores of UFPs that previously acted as condensation sites.

UFP concentrations beside busy roadways also depend strongly on emissions patterns, but the diurnal or seasonal cycle of temperature can strongly modify UFP NCs (Charron and Harrison 2003; Kuhn et al. 2005). Lower ambient temperatures favor the formation of greater numbers of the smallest particles (< 50 nm) in the roadside environment (although these particles may evaporate completely within 300 meters downwind of roadways (Zhu et al. 2004; also discussed below). Relatively low temperature and high humidity are associated with higher rates of new particle formation and slower atmospheric dispersion, indicating that UFP concentrations will generally be higher in the winter than in the summer (Sioutas et al. 2005).

Lower temperatures near the ground at night also contribute to the formation of stable atmospheric layers that trap primary pollutants near their emissions source (Herner et al. 2006); this effect can dominate UFP concentrations in regions that are not heavily influenced by photochemistry. As an example, the highest concentrations of UFP number and mass during a winter pollution event in the San Joaquin Valley were measured during the evening hours, with lower concentrations measured during the day (Herner et al. 2005).

When photochemistry is important at a location, the opposite diurnal pattern is often observed. Numerous studies have observed that total NCs are positively correlated with ozone (O_3) concentrations during the summer period, suggesting that the highest number concentrations occur on the warmest days (Sioutas et al. 2005).

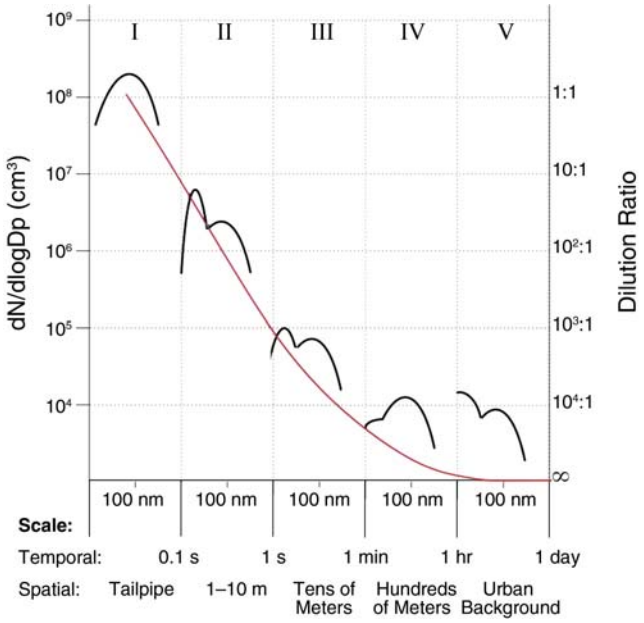

Figure 9. Typical evolution of an exhaust aerosol packet immediately before and after it leaves the tailpipe of a diesel vehicle not equipped with DPF. The initial size distribution is engine and operation condition dependent. Also, the exact time evolution of the size distribution (illustrated in columns I through V) and the dilution ratio (red line) will depend on the exhaust, traveling, and ambient conditions. In general, five phases are observed: **I)** A lognormal distribution of nonvolatile particles is produced in the engine and leaves the tailpipe. **II)** Rapid dilution with ambient air takes place that decreases the concentration of non-volatile particles. Depending on traveling speed, dilution ratio can reach 102:1 up to 104:1 during the first second after emission. In parallel, a nucleation mode of volatile particles forms in the sub-50 nm size range. **III)** Further dilution downwind of emission production takes place that decreases concentration of volatiles and leads to mild evaporation of volatile nanoparticles. **IV)** Particle concentration almost reaches background levels and nanoparticles have almost completely disappeared. **V)** A new (secondary) nanoparticle mode may be formed as a result of photochemical reactions.

Physical geography, such as topography and altitude also influence dispersion; low-lying valleys collect PM, and high elevations have greater atmospheric dispersion (Sardar et al. 2004; Zhou and Levy 2007). Urban street canyons are subject to low wind speeds and poor mixing during most times of the day, so UFP concentrations at these locations are dominated by a diurnal cycle of traffic emissions. The higher concentrations in street canyons relative to those near roads or in urban background sites were evident in the meta-analysis by Morawska and colleagues (2008) discussed earlier (see Figure 6).

Scientists have expressed increasing interest in regional-scale *nucleation events* where large numbers of particles can be formed across distances of hundreds of kilometers through nucleation processes similar to those discussed in the context of vehicle exhaust as it cools near roadways.

Nucleation events and their potential contribution to ambient UFP number concentration levels and human exposures have not been a focus of this issue of HEI Perspectives. They are discussed briefly in Sidebar 1.

Spatial Variation of Ambient UFP Concentrations

As the schematic illustration of the fate of a diesel aerosol packet in Figure 9 would suggest, observed spatial gradients of UFPs in the atmosphere are sharp, with the highest concentrations generally observed in the immediate proximity of combustion sources followed by a rapid decay. Zhu and colleagues (2002) were among the earliest investigators to monitor the change in UFP numbers and size distributions with distance from major freeways. UFP measurements were taken near a major interstate highway (freeway 710) in Los Angeles, California, where approximately 25% of the traffic came from heavy-duty diesel trucks. Figure 10 illustrates the highest NCs of the smallest sized UFPs nearest the road, followed by a rapid drop-off in concentration, transition to larger particles with increasing distance, and blending into background levels at approximately 300 meters. Subsequent studies by these investigators and others have shown that these gradients can show diurnal and seasonal patterns, for example, with the distance required to reach background extending to 500 meters or more under nighttime conditions (Zhu et al. 2006).

Karner and colleagues (2010) have now conducted a meta-analysis of 41 studies that evaluated gradients in UFPs and other traffic-related pollutants as a function of distance from roadways. Their analysis is notable because of their efforts to normalize concentrations to account for differences among studies in background concentrations (background normalization) and the distances from the edge of road at which measurements are made (edge-of-road normalization). Furthermore, the authors analyze and compare the concentration gradients for several particulate size fractions (UFPs > 3nm [UF1], > 15 nm [UF2], $PM_{2.5}$, and PM_{10}) as well as for several other traffic-related pollutants measured in the same studies (carbon monoxide [CO], EC, benzene, nitric oxide [NO], nitrogen dioxide [NO_2], NO_x, and VOCs).

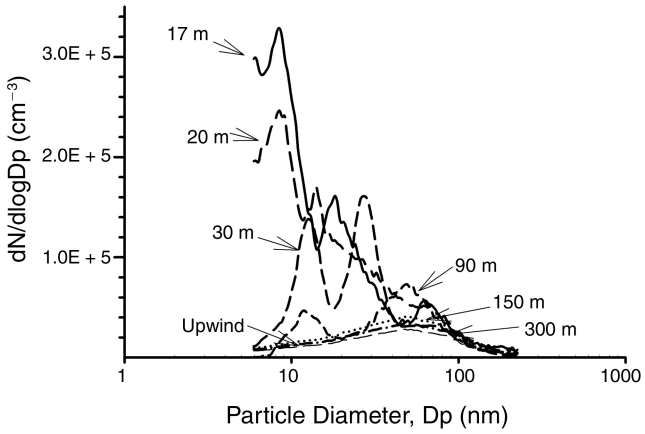

Figure 10. Ultrafine particle size distribution at different sampling locations near the 710 freeway in Los Angeles, CA. (Source: Zhu et al. 2002, reprinted with permission from Elsevier.)

Sidebar 1. Regional Nucleation Events

Regional nucleation events differ from near-roadway nucleation events because the super saturation of semivolatile compounds across the regional events is driven by the buildup of chemical reaction products rather than by the cooling of hot exhaust gases near the roadway. On a global basis, particle nucleation events are best known as an important source of cloud condensation nuclei that influence cloud properties and climate. On a regional and urban scale, nucleation can significantly increase the NC over large population centers (Stanier et al. 2004; Cheung et al. 2012). In the Stanier study for example, conducted in Pittsburg, Pennsylvania, nucleation events were observed on ~30% of the days during an extended study period.

Despite the common occurrence of regional nucleation events, the mechanisms that control nucleation rates and the chemical composition of nucleated particles are poorly understood. Venkatachari and colleagues (2007) have studied nucleation events in Flushing, New York, and suggest that concentrations of reactive oxidative species were higher in the submicron fractions relative to larger particles. Recent results from the European Integrated project on Aerosol Cloud Climate and Air Quality suggest that sulfuric acid plays a central role in most nucleation events, although some other stabilizing compound such as ammonia or amines must also play a role.

Since most epidemiologic studies have assessed associations between total ambient UFP NC and health, the specific implications of regional nucleation events, independent from other ambient UFP sources, for public health are not yet known. No epidemiologic studies have been done to isolate the effect of nucleation events on short- or long-term exposures and on health.

Figure 11 displays their results, which essentially show the percentage decrease in the concentrations of several pollutants from the roadway edge to various distances up to 500 meters. It confirms the rapid decline in the concentrations of the smallest UFP size fraction (UF1) within the first 100 meters with a more gradual decline in the UF2 size fraction to near background levels at distances of over 500 meters.

The comparisons with other pollutants are useful for indicating those pollutants whose decay patterns are similar to those of UFPs and therefore are more likely to be correlated with one another. Like the different UFP size fractions, several of the other pollutants (CO, EC, NO, NO_2, NO_x, VOCs) showed steep declines in the first 100 meters from the road. $PM_{2.5}$ and PM_{10} appear somewhat elevated nearer to roads, but generally appear to be much less spatially variable and more representative of background levels. Correlations between pollutants that show similar patterns of decay are thus higher than between those that are distributed differently (see, for example, Kaur and colleagues' study [2005] of personal exposure to UFPs, CO, and $PM_{2.5}$ at an urban intersection in London).

Given the steep gradients in UFP concentrations near sources like traffic, substantial spatial variation in UFPs can exist across a single city. In a study designed specifically to compare variation in different particle metrics, Puustinen and colleagues (2007) measured PM_{10}, $PM_{2.5}$, and total NC (using CPC) outdoors and indoors at a total of about 150 home sites spread across four European cities (Athens, Amsterdam, Birmingham, and Helsinki). Figure 12 compares variation in 24-hour average total NC and $PM_{2.5}$. Although variation was observed in both total NC and $PM_{2.5}$ across sites in the individual cities, the degree of variation tended to be greater for total NC than for $PM_{2.5}$.

The high degree of spatial variation in UFP concentrations poses both an opportunity and a challenge for scientists trying to represent population exposure to UFPs for health studies, particularly for longer-term average exposures. On the one hand, variation in concentrations of a pollutant is essential to investigate whether pollutant exposures may be related to variations in health outcomes. On the other hand, the high spatial variability makes it more difficult to rely on measurement strategies that have been adequate for more spatially homogenous particulate fractions like $PM_{2.5}$. $PM_{2.5}$ measurements taken at different locations around a city are usually better correlated with one another than are measurements of spatially heterogenous particulate fractions; exposure can therefore more reliably be represented by a city-wide average or by a central site monitor over the longer term.

For example, when the correlations between the central site and residential outdoor 24-hour concentrations of $PM_{2.5}$ and NC were compared for all sites within each of the four cities shown in Figure 12, the correlations for $PM_{2.5}$ were generally higher (city medians: 0.79–0.98) and less variable across the sites than those for total NC (city medians: 0.67–0.76) (Figure 13). For total NC, median correlations varied considerably by residential site. The greater variability in correlations for total NC measurements suggests the potential for greater error in the degree to which central site measurements represent individual exposures for UPFs relative to $PM_{2.5}$. This greater measurement error

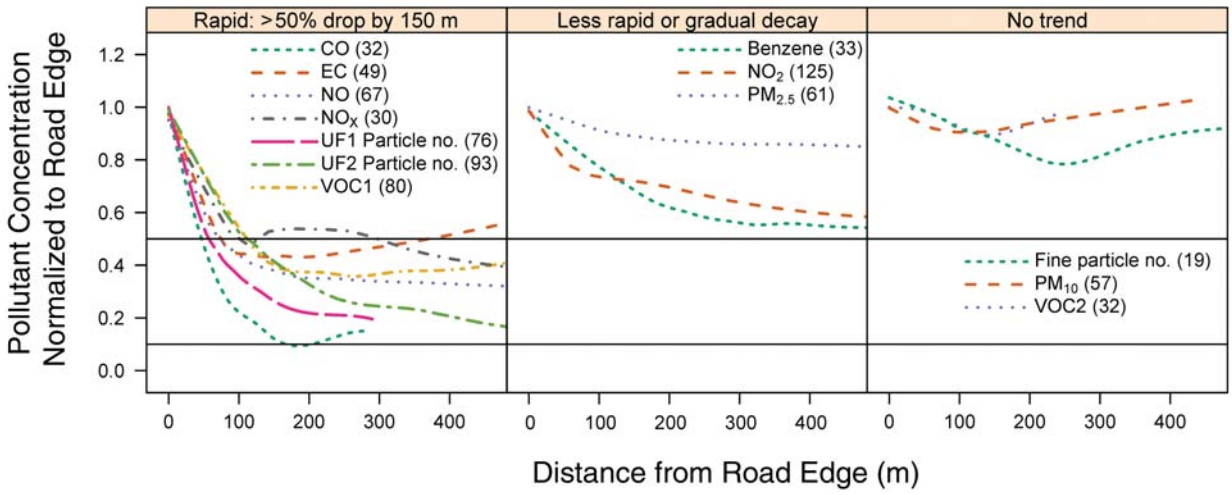

Figure 11. Local regression of road-edge normalized concentrations on distance from the edge of road. The horizontal black lines indicate reductions of 50% (0.5) and 90% (0.1) from the concentrations measured at the edge of the road. The regression sample size, *n*, is given in parentheses after each pollutant. (Source: Karner et al. 2010, reprinted with permission from the American Chemical Society.)

can limit the statistical strength of epidemiologic studies to observe any true associations that might exist. Either many more monitoring sites, or a reliable modeling strategy, would be necessary to characterize the UFP concentrations experienced in a population across a city, particularly over the longer term.

Temporal Variations Even in the case of strong differences in absolute concentrations among sites (i.e., spatial variability), particular geographic locations are influenced by common diurnal patterns and meteorological influences. Consequently, measurements at those locations may be temporally correlated. High temporal correlations among

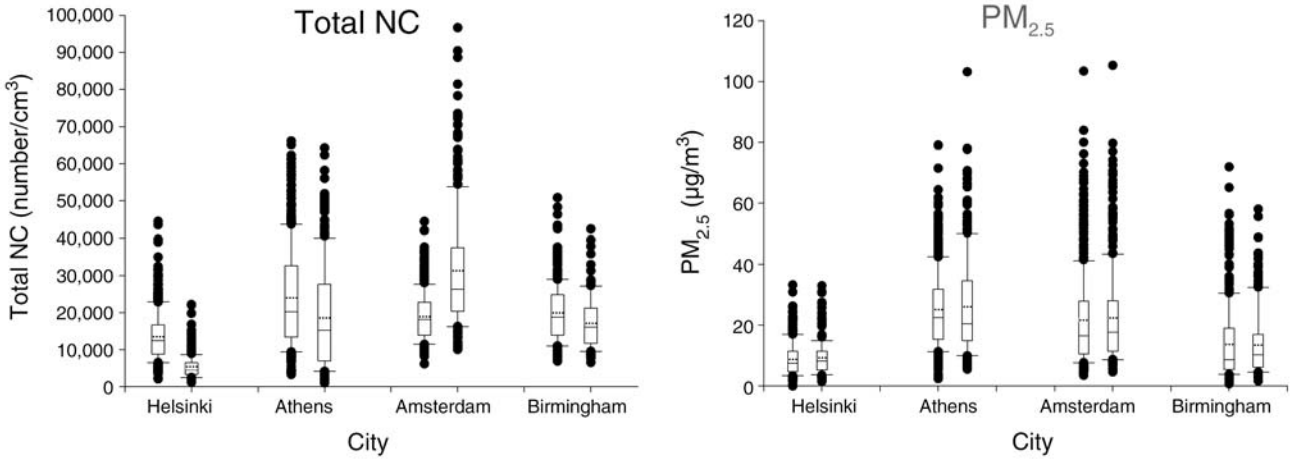

Figure 12. Distribution of 24-hour average central site (left box plot) and residential outdoor concentrations (right box plot) of total NC and $PM_{2.5}$. The center line of the box is the median, the dotted line is the mean. The outer lines of the box represent the 25th and 75th percentiles, and the whiskers represent the 10th and 90th percentiles. (Source: Puustinen et al. 2007, reprinted with permission from Elsevier.)

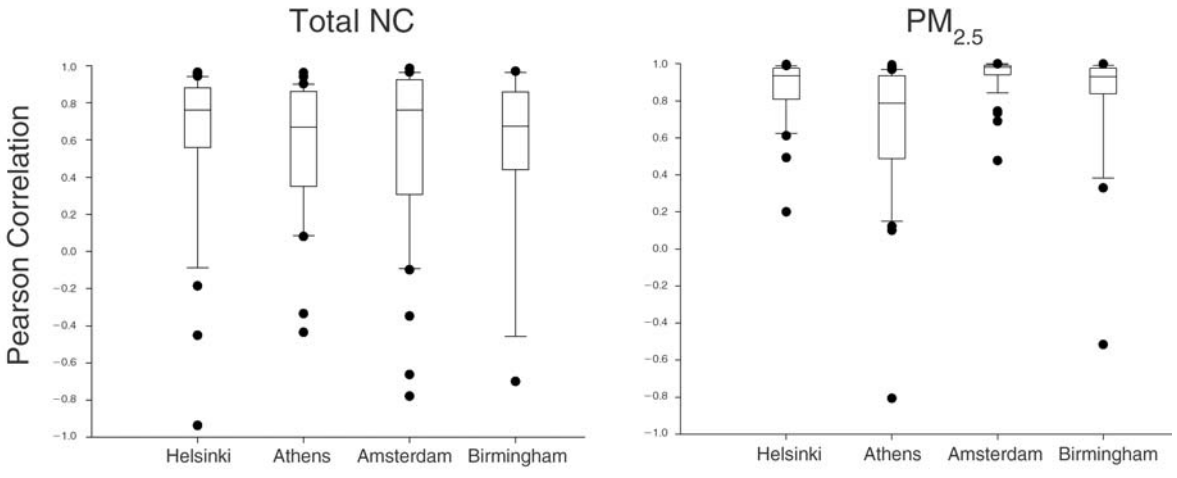

Figure 13. Distribution of individual Pearson correlation coefficients of 24-hour central site and residential outdoor concentrations for total NC and $PM_{2.5}$. The center line of the box is the median, the outer lines of the box represent the 25th and 75th percentiles, and the whiskers represent the 10th and 90th percentiles. (Source: Puustinen et al. 2007, reprinted with permission from Elsevier.)

monitoring sites indicate that ambient fixed-site monitoring may be adequate for estimation of population exposure in study designs that examine the effect of short-term changes in air quality.

The study by Puustinen and colleagues again provides a good example of high temporal correlations between sites using data from one of their study sites, a residence at an urban background site in Helsinki. Figure 14 compares the hourly variation in total number concentrations measured outdoors and indoors at their study site with those measured at the central monitoring site over the course of one week in January 2004. Other studies also suggest that correlations between monitoring sites can vary more from location to location. Cyrys and colleagues (2008) reported high correlation coefficients ($r > 0.8$) for site-to-site hourly average measurements among four traffic-affected sites in Augsburg, Germany. However, Moore and colleagues (2009), who measured total NC over a period of about one year at 14 sites in the Los Angeles area of the United States, found that the median hourly correlation coefficient across all sites varied from 0.3–0.56. They reported a 10-fold variability in hourly UFP count measurements (10,000–90,000) calculated by month. Tuch and colleagues (2006) reported a correlation of 0.31 between two locations (one roadside, one mixed industrial area) that are 1.5 km apart, across all days, in Leipzig, Germany.

Given the site-specific nature of these correlations, and their implications for how well human exposure may be measured, such correlations need to be carefully evaluated when designing studies and when reporting and interpreting study results.

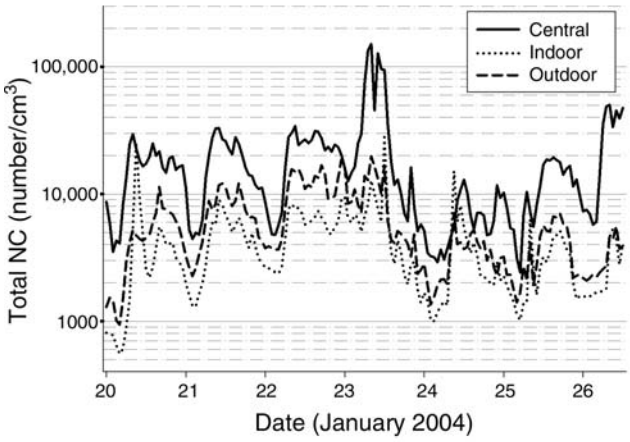

Figure 14. Illustrative example of hourly total NC measured indoors, outdoors, and at a central site for one week in January 2004 for an urban background study site in Helsinki, Finland. The correlation between hourly residential outdoor and central site concentrations was 0.89, although the concentrations were lower at the home than at the central site (ratio 0.37). (Source: Puustinen et al. 2007, reprinted with permission from Elsevier.)

Copollutant Concentrations Given their sources, UFPs are typically found in the presence of a number of other pollutants of interest to human health (e.g., CO, NO, NO_x, NO_2, EC, $PM_{2.5}$, PM_{10},) as illustrated in Figure 11. Understanding the spatial and temporal relationships between UFPs and the other pollutants with which they may covary is critical for efforts to assess their independent effects. However, copollutant exposures have not been consistently measured or reported in studies.

Some authors have suggested that NO_2 may be acting as a surrogate for other harmful pollutants in the traffic pollution mixture, including UFPs, based on associations of within-city NO_2 concentrations and adverse health effects in some epidemiologic studies (Seaton and Dennekamp 2003; WHO 2006). There is some evidence to suggest relatively high correlations between UFPs and NO_x (Sardar et al. 2004; Vinzents et al. 2005; Andersen et al. 2008b). While the recent HEI Special Report on Traffic (2010) cautioned that none of the traffic-related pollutants evaluated (including NO_2, UFP, CO, EC, or black carbon [BC]) met all the criteria for an ideal surrogate for traffic), it is possible that observed associations between health effects and spatial patterns in NO_2 related to traffic also reflect spatial patterns in traffic-related UFPs.

Consistent with the evidence provided by Karner and colleagues (2010), results from several studies seem to suggest that UFPs and $PM_{2.5}$ can be governed by different processes, so their concentrations are less likely to be well correlated. Investigators interested in the impact of local traffic restrictions on air quality in New York City found that, in contrast to $PM_{2.5}$, near-road NC (for particles 5–560 nm in diameter) varied linearly with measures of traffic flow, suggesting that they were highly influenced by traffic sources (Whitlow et al. 2011). Atmospheric processing may lead to inverse correlations between UFP concentrations and $PM_{2.5}$ concentrations, as coagulation and condensational growth moves material from the UFP size range to the accumulation mode size range over time (Chung et al. 2001; Herner et al. 2006). $PM_{2.5}$ concentrations increased by a factor of three during a winter stagnation event in central California, but UFP number and $PM_{0.1}$ mass concentrations remained relatively constant (Herner et al. 2005; Kelly et al. 2011).

Microenvironmental Exposures to UFPs

The preceding sections have focused on how well spatial and temporal patterns in ambient concentrations of

UFPs, often measured at some central location, represent those that individuals might experience at their homes. Such central site ambient measurements are the most common indicators of exposure used in epidemiologic studies. However, scientists know that an individual's total personal exposure to any air pollutant is actually a function of microenvironments, the places where people spend time during the day in which the air pollutant concentrations may differ (e.g., at home, at work, during a commute). It is also well known that concentrations in individual microenvironments can have origins both in ambient air and within the microenvironment. Though sources or precursors of UFPs within microenvironments can be substantial (Abt et al. 2000; Diapouli et al. 2008; Guo et al. 2010; Wang et al. 2010; Hovorka and Braniš 2011), and may themselves merit evaluation in health studies, they are not the focus of this document. We have focused this discussion on whether concentrations measured outdoors are in fact a good representation of human exposure to particles of ambient origin and the circumstances under which they may fall short. Such insights are important for the interpretation of health studies that may rely solely on outdoor measurements.

Ambient Contributions to Indoor Concentrations of UFPs Indoor microenvironments (e.g., home, work, schools, stores, etc.) are some of the most important determinants of personal exposure simply by virtue of the time we spend in them. Most people in the United States and in Europe spend a large fraction (90% or more) of their time indoors.

One broad approach to understanding how well ambient measurements may represent indoor exposures to particles of ambient origin is to evaluate whether the variations in ambient air concentrations are temporally or spatially correlated with those of indoor concentrations. A study by Hoek and colleagues (2008) is one of the few studies that has systematically examined such relationships for UFPs, along with other pollutants, inside a large number of homes in multiple cities. Using the same dataset as Puustinen and colleagues (2007) for 152 homes in four European cities (Amsterdam, Athens, Birmingham, and Helsinki), Hoek and colleagues analyzed the 24-hour correlations between indoor and central site concentrations for particle number, $PM_{2.5}$, soot, and sulfate over a one-week period. They reported that correlations were lower on average for particle number (0.18–0.45) than they were for the other pollutants ($PM_{2.5}$ [0.40–0.80], soot [0.64–0.92], and sulfate [0.91–0.99]), a finding that the authors suggested might be related to the higher spatial variability in ambient UFPs discussed earlier, as well as to the lower infiltration of UFPs and to the presence of indoor sources.

The results of Hoek and colleagues (2008) can be interpreted with the help of a number of other studies that have evaluated indoor and outdoor particle NC relationships, including estimating infiltration and the effect of indoor sources. These studies have reported moderately high infiltration fractions for UFPs and have noted that infiltration varies with particle size. Zhu and colleagues (2005) measured indoor UFPs in four apartments near a major freeway in Los Angeles and reported low (0.1–0.4) infiltration fractions for the smallest (10–20 nm) particles but moderate to high infiltration fractions (0.6–0.9) for 70–100 nm particles. Sarnat and colleagues (2006a) described a similar size-related pattern of infiltration fractions in 17 homes of nonsmokers in Los Angeles. These results are consistent with a study in 4 homes of nonsmokers in Boston, where Abt and colleagues (2000) reported Spearman correlations between home indoor and outdoor concentrations of 0.67 for 20–100 nm particles, 0.90 for 100–500 nm particles, and 0.83 for 700–2500 nm particles. The indoor:outdoor UFP ratios estimated from measurements in seven primary schools in Athens, Greece, ranged from 0.33 to 0.74 and were lower in general that those for PM_{10} and $PM_{2.5}$ (Diapouli et al. 2008). Studies have also suggested that the composition of particles that infiltrate to the indoors may also differ from that of outdoor particles (Sarnat et al. 2006a; Polidori et al. 2007).

Other factors can strongly influence estimated UFP infiltration rates including: air exchange or ventilation rates within buildings, presence of local outdoor sources, wind speed, season, numbers of occupants, and time of day (which may be related to indoor activities that generate particles, like cooking) (Koponen et al. 2001; Sarnat et al. 2006a; Polidori et al. 2007; Guo et al. 2008; Hoek et al. 2008; Parker et al. 2008; Weichenthal et al. 2008; Wang et al. 2010).

Collectively, these factors help explain why the relationships between outdoor and indoor concentrations of UFPs are more variable and the correlations generally lower than they are for $PM_{2.5}$ and other pollutants. They need to be considered carefully when interpreting the results of epidemiologic studies based on ambient measurements.

In-Vehicle Exposures Given the high concentrations of UFPs reported on or near roads, a large number of studies have evaluated concentrations in vehicles and as a function of mode of transport. For example, Westerdahl and colleagues (2005) reported in-vehicle total NC measurements in Los Angeles of 55,000–200,000 on freeways, 40,000 on arterial roads, and 14,000–27,000 in residential areas (background) averaged over several hours. Concentrations measured while following diesel vehicles resulted in peak concentrations of up to 800,000. In-vehicle concentrations

were also strongly dependent on the number of vehicles in front of the measurement vehicle at intersections.

Based on these and other measurements, Fruin and colleagues (2008) conducted a microenvironmental analysis and estimated that 33%–45% of total UFP exposure for Los Angeles residents was due to time spent traveling in vehicles (Fruin et al. 2008). In another study of Los Angeles freeway exposures, Zhu and colleagues (2007) estimated that a 1-hour commute accounted for 10%–50% of daily exposure to traffic-generated UFPs. Further evaluation is required to determine whether these study results of the importance of commuting exposures in the high-traffic areas around Los Angeles are representative of commuting exposures in areas with less traffic or shorter commuting times.

In-vehicle UFP concentrations can be affected by a number of factors, including temperature, wind speed, traffic counts, and numbers of passengers (Gong et al. 2009; Knibbs et al. 2011) as well as vehicle ventilation (and filtration). Standard automobile filters result in reductions of between approximately 30% and 60% in in-vehicle UFP concentrations (Zhu et al. 2007; Pui et al. 2008; Qi et al. 2008), while these percentages can be increased with advanced filters (Burtscher et al. 2008). Zhu and colleagues (2007) found that the lowest in-vehicle concentrations were observed (~85% reduction) when fans were operated on recirculation mode, and that standard filters provided reductions of ~50% for the smallest particles (7–40 nm), but that this decreased to ~20%–30% for particles in the 40–200 nm size range.

In a study in the Netherlands designed to examine the effects of transport method (car, bus, bicycle), route (high and low traffic), and fuel type (gasoline, diesel, and electric) on commuter exposures to total particle numbers and other pollutants, Zuurbier and colleagues (2010) reported no significant differences between concentrations of particle numbers inside diesel and gasoline automobiles. They suggested that this result may be a reflection of the ambient environment surrounding the automobiles and infiltration of UFPs rather than self-pollution. Commuter exposures to total particle NC in this study were lowest among those riding electric buses. Exposures via all modes of transport were elevated when following high-traffic routes relative to when travelling low-traffic routes.

Knibbs and colleagues (2011) conducted a meta-analysis of 47 in-transit studies to assess the differences in microenvironmental exposures experienced using different modes of transit (e.g., travel by bicycle, automobile, walking, ferry, rail, automobile tunnel). They reported overall trip-weighted mean UFP concentrations to be lowest for bicyclists (34,000 particles/cm^3) and highest when riding in an automobile in a traffic tunnel (300,000 particles/cm^3).

Implications for Other Countries

Most of the studies of UFP concentrations reported above have been performed in locations in the United States or Europe; they may not be representative of concentrations in other countries where the mixture of vehicle type, emission controls, and fuel composition are different. For example, Lung and colleagues (unpublished data, 2005) measured exposures of pedestrians standing at intersections in Taiwan and found variable, but much higher concentrations (123,639 particles/cm^3) than reported elsewhere. Recently, Apte and colleagues (2011) studied PM levels on the roads of Delhi, India, which have a large number of auto-rickshaws. Trip-averaged concentrations were about 280,000 particles/cm^3, which corresponded to about eight times the ambient levels. Peak concentrations of 800,000 particles/cm^3 were measured over a 10-second interval.

Modeling UFP Concentrations

In the absence of extensive monitoring networks for UFPs, investigators have begun to augment the limited monitoring data with mathematical modeling approaches for predicting spatial and temporal concentrations of UFPs over broader areas. Two methods have been explored: regional transport models and land-use regression models. In theory, numerous regional advection and dispersion models could be used to study the fate of primary UFPs (as discussed, for example, in the review by Holmes and Morawska [2006]), but special care must be exercised to specify the correct emissions rate, coagulation rate, and nucleation rate in order to represent ambient UFP NCs. Regional transport models that have incorporated these additional parameters, like the Community Multiscale Air Quality Model used the by U.S. EPA for regulatory analyses, have not been able to accurately predict UFP NCs (Elleman and Covert 2009, 2010).

As of this writing, two groups have explored land-use regression methods to model UFP concentrations in urban areas. Land-use regression models predict pollutant concentrations using relationships with land-use features such traffic intensity, building density, industrial development, and the amount of green space. Hoek and colleagues (2011) developed a land-use regression model with which they were able to explain 67% of the variability in measured total particle NC in Amsterdam. Terms in the model included the product of traffic intensity and the inverse distance to the nearest road squared (as measured in field observations), address density, and location near the port. When the variables obtained from field observations were removed, substantially less variability was explained (R^2 = 44%). The median temporal correlation between concentrations at the central site and the outdoor locations

was fairly high ($r = 0.72$). At the urban background location, there was a very low temporal correlation between $PM_{2.5}$ and particle NC ($r = 0.19$) and between particle NC and soot ($r = 0.38$). Abernethy (2012) developed a land-use regression model for UFPs using one-hour particle NC measurements (using CPC) at 80 locations and 135 geographic predictors in Vancouver, Canada. The strongest model predicted NC on the basis of length of truck routes within 50 meters, density of fast food locations within 200 meters, and natural log of the distance to the nearest port, but accounted for only half the variability in measured particle NC ($R^2 = 0.48$). Hourly median particle NCs were highly variable across the city; two-week average number concentrations were well-correlated with NO_2, NO, and NO_x concentrations at the same sites ($r = 0.64$, 0.65, and 0.70 respectively). Broader application of these models has been limited by sufficient UFP measurements with which to develop models.

Summary of Evidence Characterizing Human Exposure to Ambient UFPs

Several factors acting on the emission, transformation, and dispersion of UFPs contribute to the substantial spatial variability that exists in NCs within urban areas. This high degree of spatial variability presents an opportunity to study the potential related health effects but also suggests that epidemiologic studies of long-term exposures would require detailed spatial characterization of UFP concentrations.

Despite this spatial variability, NCs within an urban area have been shown to be reasonably correlated over time. In other words, a central monitoring site, while not accurately characterizing the concentration of UFPs elsewhere in the city, can be a reasonable measure of within- and between-day changes in UFP concentrations throughout the urban area. However, variation in the degree of correlation between sites over time may vary by city and should be confirmed before reliance on a central site monitor can be uniformly advised.

Analysis of UFP exposures by microenvironments indicates that, while indoor sources of UFPs can contribute to high indoor concentrations, contributions from outdoor sources can be substantial. Infiltration of UFPs from outdoor air varies with particle size but is relatively efficient for particles in the 70–100 nm size range. In the absence of major indoor sources, ambient UFP concentrations are moderately correlated with indoor concentrations. Where reasonably high correlations between indoor and outdoor concentrations exist, central monitoring sites may be adequate to characterize changes in personal exposure to UFPs in studies that rely on temporal variability.

Microenvironmental exposure analyses suggest that time spent in proximity to motor vehicles is a major contributor to personal exposure to ambient UFPs (NC) in urban areas. Depending upon commuting mode, route type, and duration, exposures during commuting may account for as much as 50% of an individual's daily UFP exposure.

Land-use regression and other approaches to modeling ambient UFP concentrations may eventually provide an important alternative to or complement of intensive measurement campaigns. However, further work is necessary to assess the accuracy of the models' predictions in more locations and under different conditions. Adequate measurement data will still be necessary to build models and to evaluate their performance.

CHAPTER 3. Do UFPs Affect Health? What Is the Evidence from Experimental Studies in Animals and Humans?

Concern about the possible role of UFPs in air pollution health effects was originally driven by a greater understanding of the unique physical and chemical properties of UFPs. This concern was supported by laboratory animal exposure studies suggesting that UFPs are more toxic than larger particles at an equivalent mass dose. More recently, with the development of systems for concentrating and delivering ambient particles in the UFP size range, studies to investigate the effects of human exposure to UFPs in clinical settings have become possible.

This chapter will first address the unique physical properties of UFPs, summarizing what is known about their deposition, clearance, and translocation. The physical characteristics of particles in the UFP size range profoundly affect their behavior after inhalation into the respiratory system. These characteristics are hypothesized to account in part for potential differences in toxicity in comparison with larger particles in the accumulation mode or fine particle ($PM_{2.5}$) size range.

We will then review the key findings of experimental studies in laboratory animals and humans. Our primary focus will be on studies considered most relevant to effects of ambient UFPs, defined as ≤ 100 nm in diameter. We will discuss some studies of deposition, clearance, and translocation that have used model UFPs, and some toxicologic studies involving exposures to concentrated ambient particles in the quasi-UFP range (particles < 150–180 nm).

Our focus on inhalation studies reflects our emphasis on evaluating the effects of exposure to ambient UFPs via the

normal, physiological route. For this reason, we have not taken into account studies that have exposed laboratory animals via different routes of exposure, in particular, by intratracheal instillation. Although the dose administered by this method can be controlled, particle distribution in the lung is less uniform and far from physiological (Oberdörster 2010). In addition, intratracheal instillation administers particles in a bolus, so the dose-rate is much higher than via inhalation. Furthermore, we have chosen not to review the growing body of in vitro UFP toxicology research, while nevertheless recognizing the importance of such studies in understanding specific mechanisms. We do cite select studies that help in understanding UFP disposition after inhalation.

Along with the experimental studies with humans in laboratory settings, we also discuss real-world panel studies of human exposures to ambient environments rich in UFPs (for example, in areas with heavy traffic), as long as the study design included a control exposure with reduced concentrations of UFPs.

DEPOSITION, CLEARANCE, AND TRANSLOCATION OF UFPs

To fully understand the deposition of particles entering the human body, it is useful to review the relevant anatomy of the human respiratory tract, illustrated in Figure 15. Upon inhalation, air moves through the upper respiratory tract: first through the nasal or oral cavities, then into the pharynx, or throat, and then into the larynx and upper trachea. These constitute the extra-thoracic airways. The trachea enters the thorax and splits into the two tubular bronchi, which lead to the left and right lungs. Inside the lungs, the bronchi divide repeatedly into progressively smaller tubes that end in the bronchioli, the smallest subdivision of the bronchi. Attached to the end of the bronchioli are the alveoli, tiny air sacks covered with capillaries where gas exchange takes place.

UFP deposition in the respiratory tract differs importantly from that of larger particles and can be affected by such factors as exercise, oral versus nasal breathing, disease status, and age (Daigle et al. 2003; Chalupa et al. 2004;

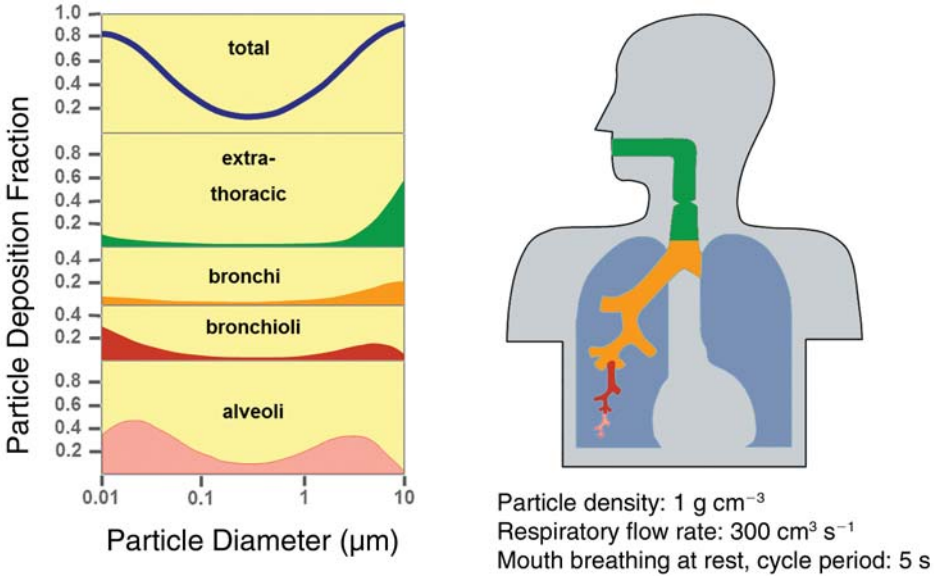

Figure 15. Total and regional deposition of inhaled particles in the adult human respiratory tract during mouth breathing at rest according to "Human Respiratory Tract Model" of the ICRP. Note particle diameter > 0.5 µm relates to the aerodynamic diameter and a particle diameter < 0.5 µm relates to the thermodynamic diameter. (Source: Kreyling et al. 2006a, Figure 2, reprinted with permission from Springer Science+Business Media.)

Geiser and Kreyling 2010). Unlike larger particles that either settle with the help of gravity or impact directly onto airway walls, UFP deposition depends largely on diffusion (Brown et al. 2002; Kreyling et al. 2006a; Möller et al. 2008).

The ICRP and others have developed models to predict the respiratory *deposition fractions* of inhaled particles based on particle characteristics and lung anatomy and physiology (ICRP 1994; Kreyling et al. 2006a,b). As shown in Figure 15, UFPs are predicted to deposit with highest efficiency in the bronchioles and alveoli, whereas larger particles (1 to 10 µm) preferentially deposit in the extrathoracic region and bronchi. A large fraction of very small particles (in the 1 to 15 nm range) also deposits in the extrathoracic airways, including the nose. The diffusional deposition probability of inhaled UFPs for the alveolar region peaks at 20–30 nm. For UFPs < 20 nm, alveolar diffusional deposition decreases, in part because increasing numbers of these small particles have already deposited in the upper airways. Furthermore, due to their ability to move via diffusion, UFPs deposit more homogeneously onto the epithelia of the various regions than fine particles or coarse particles ($PM_{2.5–10}$), and they can diffuse into nonventilated air volumes within the alveolar region.

Particle Clearance and Retention in the Respiratory Tract

Inhaled particles of all size ranges are generally cleared from different regions of the airways via both physical and chemical clearance processes (reviewed in detail in Oberdörster et al. 2005). In the bronchioles and alveoli, the major clearance mechanism results from particle phagocytosis by alveolar macrophages. If particles are not cleared from the lung, they may be retained over prolonged periods, which results in their accumulation in airway tissue.

UFPs appear to be cleared less quickly and completely from the lung than larger particles. Möller and colleagues (2008) studied the deposition of radiolabeled 100 nm particles in humans, using a shallow bolus inhalation technique that targeted deposition in the distal airways and alveoli. There was negligible particle clearance from the peripheral regions of the lung 24 hours after exposure. Findings in airways of dogs are similar (Kreyling et al. 1999).

The reasons for the slower clearance and hence prolonged retention of UFPs remain unclear. Mucociliary clearance may be less effective for UFPs, either because the particles penetrate through the mucus deep into the periciliary phase, a continuous aqueous layer of relatively low viscosity surrounding the cilia (Schürch and Gehr 1990), or they deposit in areas with a lung-lining layer in which mucous is reduced or absent. Whatever the mechanism, the lack of UFP clearance may lead to accumulation, furthering interaction of particles with lung cells, and particle translocation beyond the epithelial barrier.

Particle Translocation

UFPs have been hypothesized to have unique effects because of their potential for translocation into the blood via the lung, with subsequent transport to other organs, including the heart and brain. The mechanisms for translocation of UFPs into tissues are not well understood. Evidence suggests that UFPs may either be transported by endocytotic and exocytotic mechanisms or they may diffuse across membranes into airway cells (Geiser and Kreyling 2010); similar evidence has not been reported for fine particles. UFPs are not only taken up by macrophages but are endocytosed by epithelial lining cells to a greater extent than are larger particles (Geiser et al. 2008; Takenaka et al. 2012). In contrast to fine particles that deposit on the surface of epithelial cells, UFPs enter these cells rapidly; in this case they are no longer accessible for phagocytosis by alveolar macrophages (Rothen-Rutishauser et al. 2007). UFPs, by virtue of their small size, may form complexes with proteins in the epithelial lining fluid of the lung that enhance their movement into cells (Cedervall et al. 2007; Kreyling et al. 2007; Lynch et al. 2007). This is likely a complex process, involving protein adsorption and desorption to UFPs, and the kinetics may differ with different body and cellular fluids, organs, and tissues in ways that are not yet understood.

We will briefly review the evidence from laboratory animal and human studies for translocation of UFPs (also see Geiser and Kreyling 2010).

Laboratory Animal Studies Several experimental studies in animals have provided evidence for the translocation across the air–blood barrier of model UFPs such as gold, silver, TiO_2, polystyrene, and carbon, in the 5–100 nm size range. UFPs were found in the pulmonary vasculature and blood (Figure 16) (Berry et al. 1977; Kapp et al. 2004; Geiser et al. 2005) and in extrapulmonary organs, including the liver, spleen, kidneys, heart, brain, and reproductive organs (Takenaka et al. 2001, 2006; Kreyling et al. 2002, 2009; Oberdörster et al. 2002; Semmler et al. 2004; Semmler-Behnke et al. 2007). Estimates of the total translocated fraction of UFP range from 1%–2% of 50 nm polystyrene particles (Chen et al. 2006) to as much as 10% of 20-nm diameter radiolabeled iridium UFPs when translocation to connective tissue and bone were included (Kreyling et al. 2009). Furthermore, 20-nm iridium UFPs were poorly cleared from secondary target organs. Six months after a single one-hour UFP inhalation exposure, the total UFP fraction in all secondary target organs was

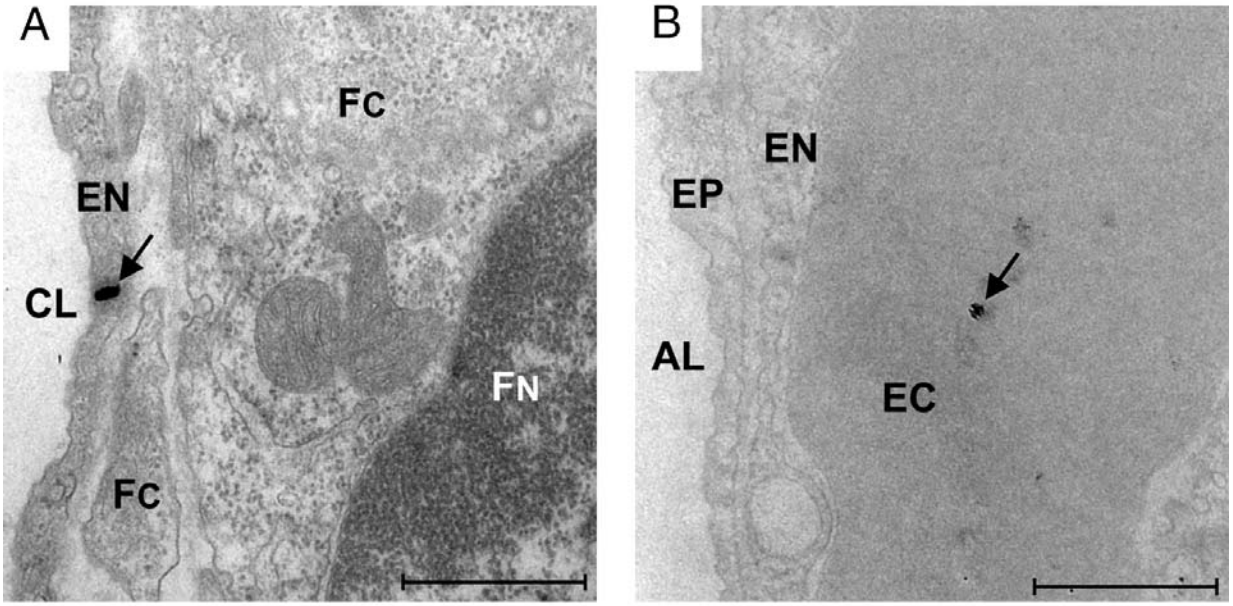

Figure 16. Images of particles (arrows) in the lung parenchyma (using energy-filtering transmission electron microscopy). Image A shows an 81 nm particle in the cytoplasm of a capillary endothelial cell (EN). **Image B** shows a 41 nm particle within an erythrocyte (EC) in the capillary lumen. (Source: Geiser et al. 2005, reproduced with permission from Environmental Health Perspectives.)

still close to 0.1% of the initial UFPs deposited in the lungs, and all organs studied still contained UFPs (Semmler et al. 2004; Semmler-Behnke et al. 2007).

Inhaled UFPs may translocate to the brain (Elder and Oberdörster 2006). UFPs that deposit in the olfactory turbinates of the nose may enter the olfactory nerve and be transported to the olfactory bulb of the brain. While UFPs may access the brain via this pathway, their effects on the central nervous system have not been evaluated in great detail (see *Neurological Responses* in the Experimental Studies section).

Human Studies We know from histopathologic evidence in studies of long-term, heavy particle exposure in smokers, coal miners, and asbestos workers (showing particle or fiber accumulation in the liver and other organs of the reticuloendothelial system) (Auerbach et al. 1980; LeFevre et al. 1982) that particles can be found in organs beyond the lung. However, these studies offer little insight as to the importance of particle size or the relative importance of inhalation and ingestion pathways and have questionable relevance to the inhalation of ambient UFPs.

Comprehensive biokinetic analysis of particle translocation is not feasible in humans for ethical and technical reasons. Thus to date, very little direct evidence of UFP accumulation and retention in organs and tissues is available from experimental human studies.

A paper by Nemmar and colleagues (2002) has been widely cited as direct evidence for UFP translocation from the airways into the circulation. However, subsequent work has failed to confirm their findings. In this study, Nemmar and colleagues exposed young volunteers to an aerosol of 5–10 nm carbon UFPs labeled with ^{99}technetium. They detected the tracer in the blood within minutes after the exposure and in the liver and stomach within an hour. They interpreted their findings to indicate that insoluble UFPs passed rapidly into the blood, and were circulated to organs throughout the body. These investigators subsequently developed a pharmacokinetic model of inhaled UFP distribution to blood and other organs based on these findings (Péry et al. 2009). However, other investigators (Mills et al. 2006; Wiebert et al. 2006a) have repeated these studies with similarly sized carbon UFPs and were unable to find evidence for particle translocation into the blood. Mills and colleagues (2006) found

that radioactive technetium leached off 4–20 nm carbon UFPs when they entered the airways, and that the radioactive moiety, rather than the particle itself, was detected rapidly in circulating blood. Möller et al. (2006) also found that the radiolabel is rapidly leached off unless it has been stabilized on the carbon UFPs. Wiebert and colleagues (2006a) did not find evidence of significant translocation of inhaled 35 nm radiolabeled carbon UFPs into the systemic blood circulation over a 24-hour period. These human studies suggest that under these specific experimental conditions, less than 1% of the inhaled dose of UFPs enters the blood and is available for translocation beyond the lung. It remains unknown what extrapulmonary burden of UFP is required to elicit health effects, and indeed whether translocation of UFPs beyond the lung is responsible for any of the health effects associated with PM exposure (Brown et al. 2002; Mills et al. 2006; Wiebert et al. 2006a,b; Möller et al. 2008).

Summary of Particle Deposition, Clearance, and Translocation

Compared with larger particles, UFPs deposit with higher efficiency, are cleared more slowly, and are retained longer. This raises the concern that chronic or repeated exposure to UFPs may lead to more accumulation within the lung of UFPs than of larger particles. Laboratory animal studies demonstrate that inhaled UFPs, but not fine or coarse particles, can translocate across the lung epithelium into the circulatory system and then be transported throughout the body where they have the potential to affect directly the cardiovascular system and other organs. UFPs depositing in the nose may also translocate via the olfactory nerve to the brain. These studies in animals also suggest that UFPs, to a greater degree than fine or coarse particles, may accumulate in organs and tissues under normal physiological conditions with the potential for long-term adverse effects. However, human studies to date have been limited and have failed to find substantial translocation of inhaled UFPs beyond the lung. It is unknown whether translocated UFPs cause or contribute to the adverse effects of PM exposure that have been observed in humans.

EXPERIMENTAL STUDIES OF ADVERSE EFFECTS OF EXPOSURE TO UFPs IN ANIMALS AND HUMANS

Experimental studies provide insight to the effects of exposure to any toxicant. The nature and level of exposure can be carefully controlled and the health endpoints chosen and evaluated against specific scientific hypotheses. For this issue of HEI Perspectives, we have focused primarily on experimental studies that involve exposures to laboratory animals and humans via inhalation, the most physiologically relevant route for exposure to ambient air pollution.

We have focused our discussion on studies of exposures to UFPs that are relevant to ambient, and especially combustion-related, UFPs in the < 100 nm size fraction. In particular:

- **Carbon UFPs.** The rationale for using these particles is that most combustion-generated particles have a carbon core, and so are representative of a major combustion-derived component of particles in ambient air, particularly those derived from diesel engines. Carbon UFPs are generated by a spark discharge of graphite electrodes; 95% of those produced consist of EC and have a median diameter of approximately 25 nm. Experiments with these particles have provided useful information about the effects of pure ultrafine carbon particles, but these particles lack the other components that are typically adsorbed to UFPs found in ambient air.
- **Ambient UFPs.** Some studies have compared the effects of exposures in contrasting environments with high versus low concentrations of ambient UFPs. A very few studies, conducted in New York State, have examined the effects of animal exposure to on-road emissions.
- **Concentrated ambient UFPs.** In order to study exposures to UFPs separately from other size fractions and at concentrations that are higher than those in ambient air, investigators have relied on UFP concentrators. These devices concentrate UFPs first by *growing* the particles in a supersaturated chamber, concentrating them using virtual impaction, and then drying them to their original size distribution. This technology becomes less efficient for particle sizes below 35–40 nm. They also usually includes a portion of particles > 100 nm, and consequently are considered quasi-UFPs. It should also be noted that an intrinsic limitation of UFP concentrator technology is the potential for chemical reactions with the condensed water, which may change the physicochemical properties of the original UFPs.

Finally, we acknowledge an entire class of experimental studies of inhalation exposures to DE in laboratory animals and in humans. Because DE from older engines has been an important source of UFP emissions, these studies are often taken to represent the effects of UFPs themselves. However, whole DE is a complex mixture of both gases and particulates, and few studies have attempted to account for the role of the various components in the health effects observed. In addition, few of those studies measured particle number. Like others who have reviewed this literature (U.S. EPA 2009; Hesterberg et al. 2011), we view the findings from this body of work to provide supportive but not direct evidence on the role of UFPs and have therefore summarized them in Sidebar 2.

Our evaluation of the studies in this chapter has focused on the set of health effects with which PM has been associated more generally in the scientific literature and for which UFPs have also been hypothesized to play a particular role given their physical and chemical characteristics:

- effects on the respiratory system, including increases in lung inflammation and allergic responses, and decreased lung function;
- effects on the cardiovascular system, including progression or exacerbations of cardiovascular disease (CVD); and
- effects on the neurological system, including increases in inflammatory responses and adverse effects on cellular function in the brain.

There are multiple pathways by which PM in general is hypothesized to exert adverse effects on various organ systems (Brook et al. 2010), but some pathways may be especially relevant for UFPs, for example, effects on the brain via translocation from the nose. Figure 17 provides a schematic of the multiple pathways via which inhaled UFPs are hypothesized to cause effects, directly or indirectly, in different organ systems. As we described in earlier sections, inhaled UFPs and their chemical constituents may act directly on the airways, the first point of contact for the particles. The indirect pathways involve mechanisms by which inhaled particles or their chemical constituents may trigger a series of responses in airway cells, in particular the synthesis of reactive oxygen species and induction of oxidative stress that may in turn result in inflammatory responses in the lungs, blood, or remote tissues. These inflammatory responses may themselves have adverse effects, including changes in the balance of the autonomic nervous system, which governs critical body functions like heart rate (HR) and respiration rate. Finally, particles may translocate from the airways to other organs and directly induce effects at sites such as the heart, liver, or brain. The animal and human studies discussed in this chapter evaluated the evidence that UFPs may be exerting influence via these various pathways using a variety of measures.

Laboratory Animal Studies

Experimental studies in animals offer certain advantages over studies in humans. Exposures can be conducted, and the toxicologic endpoints followed, over longer periods than in human studies. Endpoints can include sampling of tissues and organs. Animal studies can also include exposures during sensitive life stages such as fetal development and the extremes of age. Furthermore, special animal

Sidebar 2. Diesel Engine Exhaust — Components and Health Effects in Clinical and Animal Studies

Several controlled-exposure studies in human volunteers and rodents have examined the effects of inhaling whole diesel engine exhaust, in particular on the cardiopulmonary system. These studies are of some relevance to this issue of HEI Perspectives, because the particulate emissions from diesel engines include UFPs. Diesel particulate emissions vary in composition and in how they were formed. Nuclei mode particles are composed largely of volatile organic and sulfur compounds with smaller amounts of solid material (carbon and metallic compounds), and are generally less than 30 nm in diameter. They are the major contributor to particle number. The accumulation mode particles range in size between 30 and 500 nm and consist largely of soot (solid carbonaceous material and ash) and of adsorbed organic and sulfur compounds. These particles straddle the ultrafine and fine ranges and contribute to some extent to the UFP number (Kittelson et al. 2002). DE also contains many gases, including NO_x (primarily NO and NO_2) and carbon dioxide. The relative proportion and composition of the two particle modes and of the gaseous compounds depends on a number of factors, including testing conditions, engine type and operating condition, and fuel type.

Human clinical studies of DE have been conducted primarily in two research centers: at the University of Umea, Sweden (using either a 1990 or 1991 4-cylinder 4.5 liter Volvo diesel engine), and at the University of Washington, in Seattle (using a 2002 5.9 liter Cummins diesel engine). Details about these studies can be found in Hesterberg and colleagues (2010, 2011).

The studies investigated the effects of short-term exposure (1–2 hours) to DE on pulmonary function and immunologic and inflammatory endpoints in healthy individuals, as well as those with cardiopulmonary conditions, including asthma, metabolic syndrome, and post-myocardial infarction. Exposures were conducted at PM mass concentrations between 100 and 300 $\mu g/m^3$, but particle number or UFP concentrations were generally not reported.

These studies used differing exposure protocols and outcome measures. Nonetheless, they provide evidence that DE can cause airway inflammation and changes in systemic vascular endothelial function and thrombus formation — physiologic endpoints with relevance to both acute respiratory and cardiovascular effects. One study (*Continued next page*)

models of diseases such as asthma or atherosclerosis can be used to test hypotheses about disease-related susceptibility. The major weaknesses of these studies are the failure of many animal models to replicate all aspects of disease states and the difficulty in extrapolating findings in animals to humans. We have limited our review to studies of inhalation exposure, to studies that provide exposures specifically to UFPs, with appropriate characterization of the UFPs and, where possible, to studies that compare the effects of UFPs to other particle size ranges.

Respiratory Responses Experimental inhalation of specific kinds of model UFPs can cause airway inflammation in rats, which can be more intense than with larger (fine) particles at equal mass concentrations (Elder et al. 2000a,c; Oberdörster et al. 2000). However, inhalation in mice of carbon UFPs at concentrations considerably higher than ambient (380 μg/m³, < 100 nm) did not cause an increase of inflammatory cells in bronchoalveolar lavage fluid (Andre et al. 2006; Maier et al. 2008). Similarly, Elder and colleagues (2004b) found no airway inflammation in response to 6-hour inhalation of carbon UFPs at 150 μg/m³. A higher concentration (1.7 mg/m³ UFP, median diameter 114 nm) did produce clear signs of lung inflammation (Gilmour et al. 2004). In rodent models of respiratory compromise, such as aging rats and rats with respiratory infection, short-term inhalation of carbon UFPs enhanced pulmonary inflammation and oxidative stress (Elder et al. 2000a,c).

The lab-generated carbon UFPs used in these studies are likely to be less toxic than ambient UFPs at an equivalent concentration because ambient UFPs contain reactive organic and other chemical species. However, Elder and colleagues (2000a,b) exposed aged rats, with or without pretreatment with lipopolysaccharide or influenza virus, to freshly generated on-road aerosols for 6 to 18 hours. In general, on-road particles (which were predominantly UFPs) did not cause airway inflammation, or significantly enhance the background airway inflammation caused by the priming agents.

Several studies from investigators at University of California–Davis have explored the effects of exposure to UFPs in neonatal rats — a critical period of lung development (Pinkerton et al. 2004, 2008; Zhong et al. 2010). Specifically, the investigators evaluated the effects on neonatal lungs of exposures to combinations of laboratory-generated ultrafine iron and soot particles (20 nm in diameter, comprising both EC and OC), which were intended to model components of combustion-source–derived emissions.

Sidebar 2 (*Continued)*

found alterations of electroencephalogram signals in the frontal cortex of the brain during and up to one hour after exposure, suggesting possible effects on the central nervous system, although this has not yet been confirmed.

Both long- and short-term DE inhalation studies have also been conducted in laboratory animals, particularly rodents. Long-term exposure (up to 24 months) to high concentrations of DE (1 mg/m^3 or higher) resulted in an increase in lung tumor incidence in rats, but generally not in mice. However, long-term exposure to high levels of particles other than DE (such as carbon black and titanium dioxide) can also increase lung tumor incidence in rats, but not in other species. For this reason, the increase in carcinogenicity in the DE exposure studies has been attributed to a rat-specific *particle overload* response in the lung, rather than to a response specific to DE. Shorter exposures to DE, particularly in animal models of cardiovascular conditions such as the ApoE knockout mouse, suggest effects on cardiovascular function, such as cardiac ischemia.

Several cautions should be noted about the extrapolation of the results of these controlled human and laboratory animal studies to real-world exposures to UFPs. First, in all these studies, the particle concentrations were above those encountered in typical ambient exposures, even in heavy-traffic situations; in several rodent studies the particle concentrations were orders of magnitude higher. Second, only a few of the studies reported particle numbers, so the contribution of particles in the ultrafine range to the effects detected is uncertain. Indeed, because DE contains multiple components that may be toxic, it is not possible to conclude from these studies that effects were caused by ultrafine or larger particles, by gaseous components, or by some combination of particles and gases. Finally, regulations introduced in the United States to take effect in 2007 and beyond have mandated reductions in diesel engine emissions; the technologies developed by engine manufacturers (as well as the use of low-sulfur fuel) have substantially reduced the number and mass of particles produced by these newer engines. The health effects of these emissions, currently being investigated in HEI's Advanced Collaborative Emissions Study (ACES) program (Coordinating Research Council 2009; ACES 2012; Mauderly and McDonald 2012), are likely to differ from those of older engine emissions.

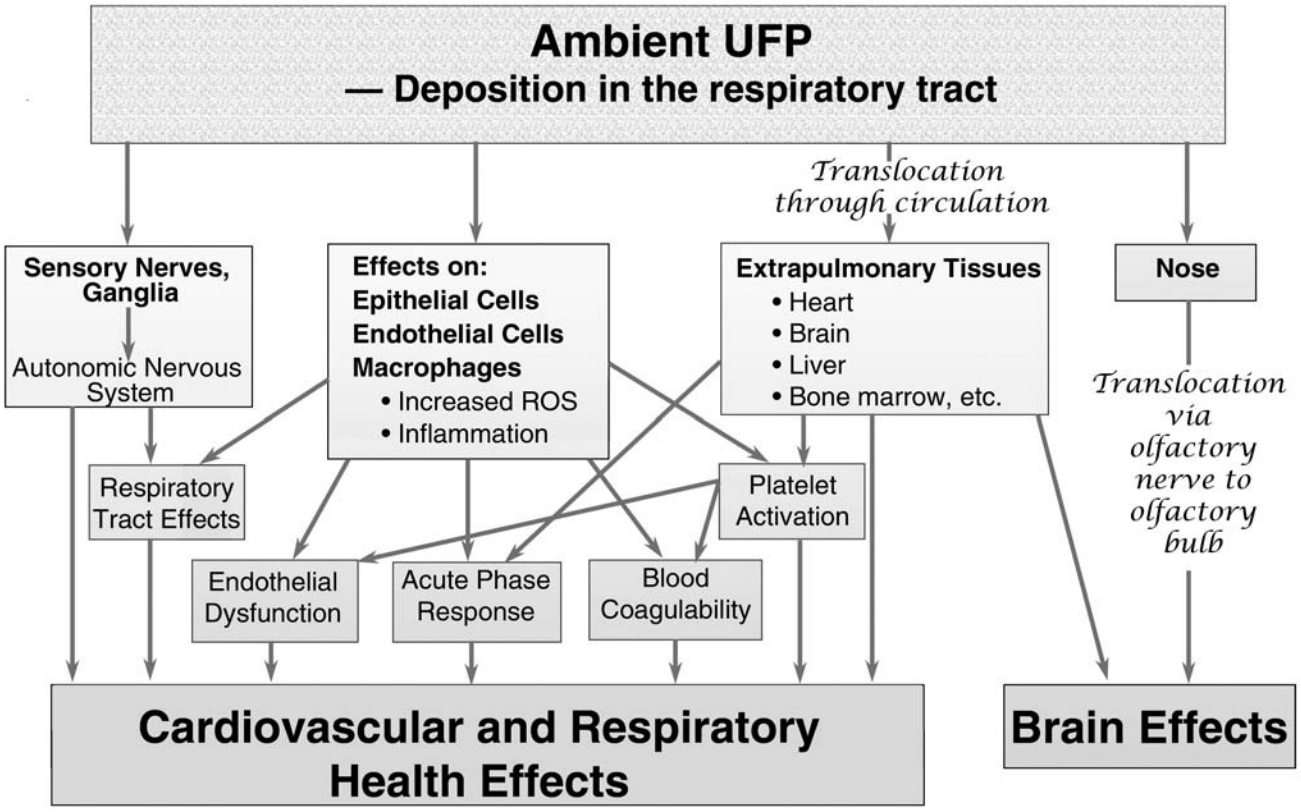

Figure 17. Hypothesized pathways via which inhalation of UFPs may lead to effects on cardiovascular and respiratory systems and on the brain.

With exposures of 243 ± 34 μg/m^3 for six hours per day for three days, cell proliferation in the alveolar region of the lung decreased, and there was evidence of oxidative injury and increases in some markers of inflammation. Lee and colleagues (2010) found changes in the architecture of the airways of adult rats that had been exposed as neonates to combustion-generated 73 nm UFP with a high OC/EC ratio; changes in lung architecture were not found after exposures to fine particles (212 nm diameter) generated with a similar OC/EC ratio.

In summary, animal studies suggest that UFPs at high concentrations have the potential to induce airway inflammation, but the concentration of *ambient* UFPs necessary to induce an inflammatory response is not known and may exceed the relatively high concentrations found on a busy roadway. Responses in different species may vary and may also differ by age of the animal. For example, some evidence suggests that neonatal exposures to UFPs may alter lung development, with the potential for lifelong consequences.

Allergic Responses The potential for UFP exposure to enhance respiratory allergic responses has been of particular interest because several early studies had shown that instillation or injection of diesel particles into animals could enhance characteristics of the allergic response (Muranaka et al. 1986; Takafuji et al. 1987; Fujimaki et al. 1997; Takano et al. 1997).

A series of studies has been conducted in California using concentrated quasi-ultrafine and fine particles collected using the versatile aerosol concentrator enrichment system (VACES). In considering the results, it is important to note that when the VACES system is used to concentrate fine particles, it includes all particles < 2.5 μm and so also includes particles in the quasi-UFP range (0.01 to < 0.18 μm).

Kleinman and colleagues used VACES in several studies of the effects of inhaling concentrated UFPs collected near roadways in a mouse model of allergy — the sensitization and challenge of BALB/c mice with the allergen, ovalbumin (OVA). In the first such study (Kleinman et al. 2005), mice

were exposed (4 hours/day, 5 days/week for 2 weeks) to either concentrated quasi-UFPs (< 150 nm) or concentrated fine particles (< 2.5 μm) collected at different distances (50 m or 150 m) from a roadway used by many diesel trucks. Particle mass in both quasi-UFP and fine particle groups averaged approximately 400 $\mu g/m^3$, and particle counts averaged 200,000/cm^3. No differences in effects were found between exposure to concentrated fine particles (including UFPs) or to UFPs alone. However, mice exposed to either size fraction of concentrated particles at 50 meters from the roadway showed greater increases in markers of inflammation and of the allergic response (immunoglobulin [Ig]E, IgG1[the mouse equivalent of human IgG4, which is elevated in allergic responses], interleukin [IL]-5, and eosinophils) compared to mice exposed at 150 meters from the roadway.

Similar results were found in a follow-up study by the same investigators (Kleinman et al. 2007); IL-5 and IgG1 levels were increased in mice exposed nearest to the road (50 m) but not at the greater distance (150 m) from the road. These increases were associated with EC and OC components of both fine particles and UFPs, suggesting the importance not just of particle size but of particle composition. Li and colleagues (2010) also found that exposure to concentrated ambient quasi-UFPs, (< 180 nm) collected close to a freeway in Los Angeles, enhanced the secondary or memory-type response in this animal model: exposure to UFPs increased features of the allergic response (influx of eosinophils into the airways, increased levels OVA-specific IgE and IgG1, and enhanced expression of the cytokine genes IL-5 and IL-13 in the lung). Exposure to UFPs in this study also enhanced inflammatory-type responses (enhanced expression of IL-17a and influx of neutrophils in the lung).

In addition, in a similar OVA mouse model of allergy, several studies have shown that 24-hour exposures to carbon UFPs (< 100 nm) potentiated the effects of lung allergic inflammation (Alessandrini et al. 2006, 2008; Maier et al. 2008). Alessandrini and colleagues (2006) showed that 24-hour exposure to 526 $\mu g/m^3$ 35 nm carbon UFPs up to 96 hours before OVA challenge enhanced bronchoalveolar lavage inflammatory cell infiltrate and IL-4, IL-5, and IL-13 levels, as well as mucus production in the airways. Exposure to the same concentration of carbon UFPs 24 or 72 hours after OVA challenge had much milder effects on airway inflammation, suggesting that sensitized animals are more sensitive to the effects of exposure to UFPs if exposed before allergen challenge. Evaluating particle deposition in the BALB/c OVA sensitization and challenge mouse model, Alessandrini and colleagues (2008) found that compared to nonsensitized mice, OVA-sensitized mice exposed for one hour to ultrafine iridium particles radiolabeled with ^{192}Ir (UF-Ir) before OVA challenge showed a 21% relative increase in the total UF-Ir deposited fraction. When inhalation of UF-Ir was performed after allergen challenge, no differences in total deposited fraction or extrathoracic deposition or regional particle deposition were detected between sensitized and nonsensitized mice.

Alessandrini and colleagues (2009) confirmed that 24-hour exposure to 504 $\mu g/m^3$ 35 nm carbon UFPs before OVA challenge enhanced the markers of inflammation they had detected previously, but also found that levels of 8-isoprostane, a marker of lipid peroxidation and oxidative stress, and NF-κB, a transcription factor that activates genes involved in inflammatory and other responses, were also enhanced. These studies provide support for the hypothesis that UFP exposure may enhance components of the allergic response, perhaps by facilitating the entry or processing of allergen that has deposited in the airway. However, the exposure concentrations in these studies were quite high, and it is uncertain whether these effects occur at concentrations more relevant to ambient levels.

Cardiovascular Responses The relatively few animal studies that have evaluated cardiovascular responses provide some evidence of UFP effects on the cardiovascular system but differ in the types of UFP exposures used and the outcomes examined.

Two studies have found that rodents exposed to carbon UFPs at concentrations relevant to ambient levels (100–200 $\mu g/m^3$, $1–5 \times 10^6$ particles/cm^3) for as little as 24 hours showed changes in cardiovascular endpoints. Exposure to carbon UFPs (median diameter 72–74 nm; aggregate: 80% mass < 100 nm) for 24 hours showed thrombogenic effects in the microcirculation of healthy mice without any significant sign of inflammation in the respiratory tract (Khandoga et al. 2010). Furthermore, a mild but consistent increase in HR and a significant decrease in HR variability were found during inhalation of carbon UFPs (median diameter 38 nm) (Harder et al. 2005).

Araujo and colleagues (2008) have conducted one of the few studies designed to compare directly the effects of exposure to UFPs (albeit quasi-UFP < 180 nm) and $PM_{2.5}$ (containing concentrated UFPs). It is also one of the few animal studies of cardiovascular outcomes to compare the composition of the two size fractions. Using particles concentrated by the VACES from ambient air close to a Los Angeles freeway, Araujo and colleagues (2008) compared the effects of exposures to quasi-UFPs and fine PM at

approximately the same NC (~5 × 10^5 particles/cm^3). Apo E knockout mice — a strain that develops atherosclerosis more rapidly than normal mice (particularly if fed on a high-fat chow) — developed 25% and 55% larger atherosclerotic lesions when exposed to concentrated UFPs (5 hr/day, 3 days per week for 5 weeks) compared with $PM_{2.5}$ and with filtered air, respectively (see Figure 18).

Exploring the possible mechanisms by which particles might affect the development of atherosclerosis, the investigators found that, compared with exposure to $PM_{2.5}$, exposure to the quasi-UFPs resulted in a decrease in the anti-inflammatory capacity of plasma high-density lipoprotein and in increased measures of systemic oxidative stress.

It remains unclear whether differences in particle composition could at least partially explain these findings. Figure 19 summarizes the percentage contribution by mass of metals, nitrates, sulfates, EC, and OC in each size fraction. The quasi-UFP fraction was enriched in OC, and to a lesser degree in EC, compared with the $PM_{2.5}$ fraction. Further exploration of the implications of composition is needed.

Elder and colleagues (2004a; 2007) have conducted the only studies of rats exposed by inhalation to ambient particles, predominantly UFPs, while being driven along a major highway (I-90 in New York State). They studied both pulmonary and cardiovascular endpoints. Elder and colleagues (2004a) found that a 6-hour on-road exposure (1–3 × 10^5 particles/cm^3) of older rats (21 months), with and without prechallenges using either endotoxin (lipopolysaccharide) or influenza virus, was associated with enhanced plasma endothelin-2, which causes constriction of arteries and increases in blood pressure (BP). Elder and colleagues (2007) later evaluated a similar 6-hour on-road exposure (count median diameter 15–20 nm) on the HR and heart-rate variability (HRV) of spontaneously hypertensive rats. Rats exposed to the highway aerosol had a lower HR compared to rats exposed to clean air, an effect that persisted after exposure. In addition, exposure to the highway aerosol affected several HRV parameters that suggested an effect on the autonomic nervous system, with a shift from parasympathetic to sympathetic (fight or flight) influences.

This collection of animal studies provides evidence of cardiovascular effects associated with UFPs of different size fractions; the study by Araujo and colleagues (2008) suggests that particles in the quasi-UFP fraction alone have a greater effect than an equivalent number of fine particles on the progression of atherosclerosis. However, the animal data are insufficient to provide clear evidence that UFPs have cardiovascular effects that differ from those of fine particles.

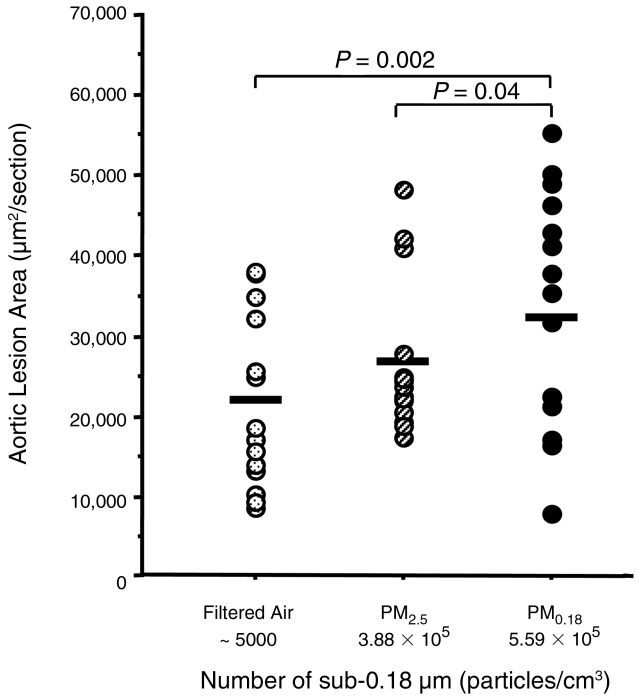

Figure 18. Mouse model of atherosclerosis: Near-roadway concentrated fine particulate matter ($PM_{2.5}$) and quasi-ultrafine particles (< $PM_{0.18}$) compared with filtered air. (Source: Araujo et al. 2008, reprinted with permission from Wolters Kluwer Health.)

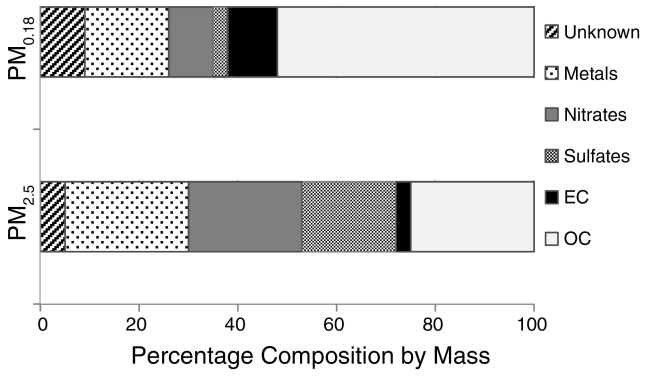

Figure 19. Comparison of the chemical composition of concentrated quasi-ultrafine ($PM_{0.18}$) and fine particulate matter ($PM_{2.5}$) in the previous study of mouse atherosclerosis in Figure 18. (Source: Araujo et al. 2008, adapted with permission from Wolters Kluwer Health.)

Neurological Responses A small number of studies have looked at neurological responses in rodents after exposures to ambient UFPs or more specifically, to concentrated quasi-UFPs (< 180 nm). As discussed earlier, a limitation of these studies from the standpoint of this issue of HEI Perspectives is that they involve exposures to particles that are larger than the < 100 nm definition for UFPs. However, a strength is that at least some of these studies also conducted direct comparisons with particles in the $PM_{2.5}$ size range. Collectively, these studies provide some indication that, compared with filtered air, exposure to quasi-UFPs in the vicinity of major freeways induces allergenic responses, inflammatory responses, or both in the brain. However, in studies with parallel exposures to fine particles, similar inflammatory responses were observed.

Campbell and colleagues (2005), studied the brains of the OVA-sensitized BALB/c mice that had been exposed to filtered air, concentrated quasi-UFPs, or the fine particles collected at varying distances from the roadway in the study by Kleinman and colleagues (2005) (discussed earlier in the *Allergic Responses* section). The brains of these mice showed increased levels of mediators associated with the induction of inflammatory responses — interleukin-1 alpha (IL-1α) and tumor necrosis factor alpha (TNFα), and of the transcription factor NF-κB. Increases in levels of IL-1α and TNFα were also detected by Campbell and colleagues (2009) in the brains of ApoE knockout mice after exposure to either quasi-UFPs or fine PM.

Kleinman and colleagues (2008) found that Apo E knockout mice exposed to concentrated UFPs (4- or 15-fold) from ambient air close to a freeway in central Los Angeles for 5 hours/day, 3 days/week for 5 weeks showed changes in brain cell function compared to cells from filtered air controls. Changes included a dose-related increase in nuclear translocation of NF-κB and in another transcription factor, AP-1, that are associated with the induction of immune and inflammatory responses. Exposure to quasi-UFPs also activated NF-κB and AP-1 in the brains of the ApoE knockout mice reported by Campbell and colleagues (2009). Kleinman and colleagues (2008) also found that the lower concentration of concentrated UFPs also increased the activation of a kinase, JNK, which participates in one of the intracellular cascades that leads to the activation of these transcription factors. In addition, UFP-exposed mice showed increased expression of glial fibrillary acidic protein, a molecule expressed on the surface of glial cells. These findings suggest that exposure to concentrated ambient UFPs near a roadway has the potential to induce inflammation in the brain.

Summary of Animal Studies These studies suggest that traffic-related UFPs may enhance allergic responses in allergen-sensitized animals. Furthermore, quasi-UFPs may enhance the progression of atherosclerosis in ApoE knockout mice, and may influence autonomic control of the heart in aged rats. Markers of inflammation in the brain increased after exposure to concentrated traffic-related quasi-UFPs, but similar increases were also observed with exposure to concentrated $PM_{2.5}$. These are intriguing findings, suggesting that there may be extrapulmonary effects of traffic-related UFPs. However, the findings must be considered preliminary; they require confirmation in other models and laboratories.

Experimental Human Exposures to UFPs

Human exposure studies of various designs have constituted an important set of experiments for understanding the health effects of air pollution and have played an important role in establishing rational ambient air pollution standards. Human clinical studies, studies of human exposure to controlled atmospheres usually performed within a specially designed exposure facility or chamber, have several strengths and weaknesses that have been discussed at length in previous reviews (Frampton 2006; Langrish et al. 2011). A major strength, of course, is that humans are the species of most interest. They can be exposed to particles via a physiologically relevant route such as oral or oro-nasal breathing using exposure atmospheres that can be carefully controlled and characterized. Different exposure scenarios can be designed to compare effects, in the same person, of exposure to particles of different size ranges when the individual is engaged in different levels of activity. Exercise for example, increases breathing and can therefore affect particle intake, and deposition (see section, *Deposition, Clearance, and Translocation of UFPs*). Under carefully controlled conditions, the effects of exposures can be evaluated in potentially susceptible subpopulations, such as those with cardiorespiratory diseases, asthma, and diabetes.

However, such experiments are generally limited to short-term exposures (a few hours maximum) and so do not provide insight into potential chronic effects. Ethical and safety considerations prevent the study of those most susceptible to pollutant health effects, such as people with severe airway constriction or with CVD, and limit the use of invasive outcome measures.

Clinical studies of UFPs have involved unique technical challenges. Prior to the development of UFP concentrators 10–15 years ago, there was no way to study ambient exposures to UFPs that did not include other particles and gases. As indicated earlier, because UFPs have so little

mass even the current generation of UFP concentrators does not efficiently concentrate UFPs smaller than about 35–40 nm. UFPs can be generated in the laboratory, but cannot be collected and resuspended for later exposure because the UFPs agglomerate into larger particles. For these reasons, there have been relatively few human controlled-inhalation studies of UFP exposure, and the exposure atmospheres of those studies are not entirely representative of ambient UFPs. Nonetheless, with these caveats in mind, the limited number of such studies has provided valuable information.

To move beyond some of the limitations of clinical studies, we have broadened our discussion of experimental studies of controlled human exposure to include panel studies of exposures to real-world environments, such as walking along a busy street. We have included the latter studies provided they included both an assessment of exposure to UFPs, such as particle number counts, and a cleaner air exposure as a control. These study designs involve other challenges but can also offer additional insights.

Respiratory Responses Respiratory outcome measures include pulmonary function (in particular, forced expiratory volume in 1 second [FEV_1], forced vital capacity [FVC], and peak expiratory flow [PEF]). Pulmonary function testing is used to diagnose and monitor respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD), and reductions in FEV_1 correlate with impairments in physical functional status. Even transient reductions in lung function, if accompanied by symptoms, are considered to be adverse health effects (American Thoracic Society 2000). Other respiratory measures include an influx of inflammatory cells into the airways and markers of airway injury or inflammation in exhaled air.

Respiratory responses of UFPs have been studied in clinical chamber studies using both laboratory-generated UFPs and UFP concentrators, as well as in real-world exposure settings enriched in UFPs. While real-world exposures have shown some respiratory effects, most chamber studies have not.

Chamber Studies — Carbon UFPs A group in Rochester, New York, led by Drs. Frampton and Utell, has published a series of studies (Frampton et al. 2004; Pietropaoli et al. 2004a,b; Stewart et al. 2010) that focus on the effects of controlled inhalation via mouthpiece of laboratory-generated carbon UFPs. These experiments provided useful information about the effects of pure carbon UFPs, but in the absence of adsorbed components that would be attached to UFPs found in ambient air. In aggregate, these studies show little evidence for acute effects of carbon UFPs on lung function. One study of exposure to 50 $\mu g/m^3$ carbon UFPs for two hours with intermittent exercise found small, marginally significant reductions in the maximal midexpiratory flow rate (about −5% relative to filtered air), suggesting mild obstructive or small airways effects (Pietropaoli et al. 2004a). However, there were no significant effects on FEV_1, and none of the other carbon UFP inhalation studies showed lung function effects (Stewart et al. 2010). Similarly, there was no evidence for increased airway inflammation, assessed by a lack of changes in markers in induced sputum or in the level of exhaled NO.

In a comparative study of ultrafine and fine particles, the investigators exposed resting healthy subjects to clean air, to 500 $\mu g/m^3$ of ultrafine zinc oxide particles, and to 500 $\mu g/m^3$ of ultrafine zinc oxide particles that were allowed to agglomerate in an aging chamber to the fine particle size range (Beckett et al. 2005). Zinc oxide particles can be generated by welding processes, and in occupational settings their inhalation can lead to a systemic inflammatory response known as metal fume fever. However, no effects were detected in any of the physiological, airway or systemic inflammatory, or cardiac endpoints examined for exposure to particles of either size range.

Chamber Studies — Concentrated UFPs Only a few studies have utilized concentrated ambient UFPs to examine health effects in humans. As with chamber studies of exposure to carbon UFPs, they have provided weak evidence of UFP effects on respiratory outcomes.

Gong and colleagues (2008) exposed healthy and asthmatic volunteers to filtered air or to 7- to 8-fold concentrated quasi-UFPs (mean particle count 145,000/cm^3, mean mass concentration 100 $\mu g/m^3$, and diameter < 180 nm) for two hours with intermittent exercise in a chamber. The UFPs were collected in a Los Angeles suburb that has heavily-traveled roadways. Exposure to UFPs was associated with a 0.5% mean reduction in arterial oxygen saturation and a 2% mean reduction in FEV_1 the morning after exposure, estimated across all subjects. However, there was no evidence for increased airway inflammation by analysis of induced sputum or exhaled air. Responses in healthy and asthmatic subjects were similar.

Samet and colleagues (2007, 2009) compared the effects of concentrated ambient quasi-UFPs ($PM_{< 0.16\ \mu m}$), $PM_{2.5}$, and coarse particles ($PM_{2.5\text{-}10}$) delivered to young, intermittently exercising human volunteers at the U.S. EPA lab in Chapel Hill, North Carolina. These studies used the Harvard particle concentrator systems which, in contrast to the VACES system, delivers fine and coarse particles that do not include UFPs. Concentrated quasi-UFPs ($1.52 \times 10^5 \pm 1.65 \times 10^5$ particles/cm^3) had no effect on pulmonary function or on the influx of inflammatory cells

in bronchoalveolar lavage fluid 18 hours after the exposure, whereas fine and coarse particles caused a modest degree of airway inflammation. Both the Gong and Samet studies also examined multiple cardiovascular endpoints, which are summarized in a later section on cardiovascular responses.

Real-World Ambient Air Studies A series of panel studies compared health responses in individuals exposed to high numbers of UFPs (e.g., high traffic intensity) with those in individuals exposed to cleaner air (e.g., low traffic intensity). An advantage of the study design is the use of realistic exposures to ambient UFPs. However, these exposures necessarily involve mixtures of pollutants, making it difficult to attribute effects to any single pollutant type. Such exposures cannot be blinded, so expectations on the part of subjects or investigators could confound the results. Furthermore, the exposure settings likely differ in ways other than pollutant concentrations. For example, traffic noise, odor, and visual stimuli may differ between the experimental and control exposure settings, with unpredictable results on outcome measures.

Two publications examined the results of a study of lung function and inflammatory responses in 60 subjects with mild or moderate asthma who walked for two hours on separate occasions on Oxford Street and on Hyde Park in London (McCreanor et al. 2007; Zhang et al. 2009). Oxford Street is a busy street on which only diesel vehicles are allowed. Exposures were characterized in real time, including total particle number counts using a CPC. The Oxford Street exposures had higher particle counts compared with the Hyde Park exposures, and they were associated with greater declines in FEV_1 and FVC, increased markers of airway inflammation in induced sputum, and a decline in the pH of exhaled breath condensate. These findings indicate that the Oxford Street exposures worsened markers of asthma in these subjects, although self-reported symptoms of asthma did not change (Zhang et al. 2009). Respiratory changes were statistically most strongly associated with UFP exposures, although there were also significant associations with exposure to NO_2. However, in multiple-pollutant models, particle number counts and EC concentrations were most consistently associated with effects.

Rundell and colleagues (2007, 2008) have studied lung function and markers of inflammation in healthy young volunteers exercising in environments with contrasting total NCs ($NC_{0.02–1.0}$ as measured by CPC). In the 2008 study, subjects performed vigorous 30 minute running trials, either on an inner campus loop free of vehicle traffic with low particle counts (mean 7382 particles/cm^3), or on a soccer field and trail within 50 meters of a major highway with high particle counts (mean 252,290 particles/cm^3). Concentrations of CO, NO_2, and O_3 were comparable in the two environments. The near-traffic exposures were associated with statistically significant airway effects, including reductions in lung function, alveolar NO concentrations, and nitrate, and with increased levels of malondialdehyde, a marker of oxidative stress in exhaled breath condensate. These findings were interpreted as suggesting pollutant-induced airway effects, but the changes cannot be attributed specifically to UFPs.

Similar studies have been conducted by Strak and colleagues (2010) with bicyclists in Europe and have detected little evidence of an UFP effect on lung function or measures of inflammation. These investigators evaluated a marker of airway inflammation (exhaled NO), and lung function (FEV_1, FVC, and PEF) in 12 healthy adults who cycled on a low- and a high-traffic intensity route in Utrecht, the Netherlands. As expected, particle number counts were higher on the high-traffic intensity route (41,097 particles/cm^3) than on the low-traffic intensity route (27,028 particles/cm^3); however, the PM_{10} concentrations were similar on both routes. There were no statistically significant relationships between the exposures and the outcome measures. In a study in Antwerp with a larger number of healthy volunteers (38), Jacobs and colleagues (2010) compared the effects of bicycling in traffic (28,867 particles/cm^3) and bicycling in a laboratory with filtered air (496 particles/cm^3). There was no effect of exposure on exhaled NO, which is considered a measure of airway inflammation. Bicycling in traffic was associated with an increase in blood neutrophils, but no change was observed in the other blood markers tested.

A recent study of cyclists in Ottawa, Canada did not find strong associations of total NC or BC, NO_2, or O_3 with respiratory outcomes; associations with exhaled NO and pulmonary function measures were inconsistent across endpoints, lags, and pollutants (Weichenthal et al. 2011). In another recent series of studies of commuters' exposures to air pollution in traffic, Zuurbier and colleagues found various associations of total NC with effects on lung function (FEV1, PEF), exhaled NO, and airway resistance in 34 healthy nonsmoking adults directly after and 6-hours after (depending on the endpoint measured) 2-hour commutes by bus, car, or bicycle; select associations with PM_{10} and soot were also observed (Zuurbier et al. 2010, 2011b). Estimated effects were not consistent for other lung function parameters, respiratory symptoms, and blood markers of inflammation and coagulation (Zuurbier et al. 2011a,b). Potential confounding by stress, noise, or both was not assessed in these studies.

Klepczynska Nyström and colleagues (2010) examined the respiratory effects of exposure for two hours in a subway tunnel in Stockholm, Sweden, using an office environment as a clean-air control. Blood sampling and bronchoscopy were performed 14 hours after exposure. Pollutants measured in the tunnel and in the control environment included not only UFPs (mean $NC_{< 100\ nm}$), but also $PM_{2.5}$, PM_{10}, NO, and NO_2. The $NC_{< 100\ nm}$ in tunnels was 110,000 particles/cm^3 versus 8,283 particles/cm^3 in the control environment. The investigators found no effects on lung function or airway inflammation associated with exposures in the subway. However, they did observe statistically significant increases in levels of blood fibrinogen and regulatory T-lymphocytes after the subway exposure.

Summary of Human Respiratory Responses Experimental studies with human subjects include a spectrum of exposures, from laboratory-generated model UFPs and concentrated ambient particles delivered in specially designed chambers, to ambient exposures in real-world settings. Relatively few studies have compared the effects of particles of different size fractions or accounted for the presence of other copollutants.

The small number of experimental studies conducted to date show a range of findings on respiratory outcomes, from reductions in lung function and increases in airway inflammation to no effects. In the one study that compared respiratory responses to UFPs, fine particles, and coarse particles, pulmonary inflammation was observed with fine and coarse particles but not with UFPs; no changes were observed in lung function for any exposure. Similarly, the laboratory-generated carbon UFP studies found no evidence for airway inflammatory effects and no convincing effects on lung function. In contrast, some of the real-world studies found changes in lung function and airway inflammatory markers, particularly in subjects with asthma, while others did not. While these diverse findings may reflect some of the inherent limitations of these study designs (e.g., small sample size, short durations of exposure, subjects who are not blinded to the type of exposure they receive), they raise additional questions about the potential importance of the overall mixture in which UFP exposures occur.

Cardiovascular Responses The role of exposures to PM in the development or exacerbation of CVD and in cardiovascular mortality in humans has been of considerable research interest (see, for example, the review by Brook et al. 2010). The following section provides a summary of the contributions from experimental, controlled human exposure studies to the base of evidence on UFPs.

Chamber Studies — Carbon UFPs The studies of laboratory-generated carbon UFP inhalation have suggested effects on both pulmonary and systemic vascular function in both healthy and asthmatic people. Inhalation of 10 or 25 $\mu g/m^3$ of carbon UFPs (~2×10^6 and ~7×10^6 particles/cm^3, respectively) during intermittent exercise showed concentration-related attenuation of the exercise-induced increase in the peripheral blood leukocyte surface expression of adhesion molecules (Frampton et al. 2004, 2006). This finding was considered consistent with transient pulmonary vascular effects of carbon UFP exposure. It was also supported by studies of 50 $\mu g/m^3$ carbon UFPs showing reductions in the diffusing capacity for CO approximately 24 hours after a 2-hour exposure (Pietropaoli et al. 2004a). Taken together with the blood leukocyte findings, these results suggest that carbon UFP exposure transiently reduces pulmonary capillary blood volume, and thus affects pulmonary circulatory function. Although the significance of this finding is unknown, such an effect, if repeated and persistent, could contribute to remodeling of the pulmonary circulation and the development of pulmonary hypertension.

With regard to effects on the systemic circulation, a study in healthy exercising people inhaling carbon UFPs at 50 $\mu g/m^3$ (Shah et al. 2008) found that carbon UFPs completely inhibited the expected exercise-associated increase in peak hyperemic forearm blood flow (a measure of systemic vascular responsiveness with relevance for cardiac coronary artery disease) 3.5 hours after exposure. One potential mechanism for reduction in vascular responsiveness is a reduction in the circulatory bioavailability of endogenous NO, which causes relaxation of vascular smooth muscle. The investigators observed reduced plasma nitrate concentrations (a product of NO oxidation) in comparison with a control filtered air exposure. These findings support the hypothesis that inhalation of carbon UFPs impairs systemic vascular function and reduces NO bioavailability. A study of people with type 2 diabetes, exposed at rest to 50 $\mu g/m^3$ carbon UFPs, showed changes in markers associated with enhanced blood coagulation — an increase in plasma von Willibrand factor and an increase in markers of platelet activation (Stewart et al. 2010).

A recent study from the same research group focused on cardiac changes measured by electrocardiogram (ECG) in young healthy adults after exposure to 10 and 25 $\mu g/m^3$ carbon UFPs (Zareba et al. 2009). Changes were generally small and not significant, but the authors felt that there was a trend in HRV that indicated an increase in parasympathetic tone, the arm of the autonomic nervous system involved in slowing down the HR. The health implications of transient changes in HRV in young healthy people are not clear.

Chamber Studies — Concentrated UFPs The studies of Samet and colleagues (2007, 2009) comparing the effects of exposure to concentrated UFPs, fine particles, and coarse particles on respiratory endpoints also examined several indicators of cardiovascular function. As illustrated in Figure 20, exposure to concentrated UFPs increased D-dimer in blood, indicating activation of coagulation, and also transiently increased blood lipids. Continuous ECG monitoring revealed increases in markers of HRV and variance in duration of the QT interval (Samet et al. 2009).

HRV was also measured in the study by Gong and colleagues (2008) in which healthy and asthmatic volunteers were exposed to concentrated UFPs in a Los Angeles suburb (for exposure details, refer to the discussion in the *Respiratory Responses* section). Exposure to UFPs was associated with a transient slight decrease in low-frequency power, without changes in other measures of HRV. Responses in people with asthma were similar to responses in people without asthma.

A recent study (Mills et al. 2011b) was designed to determine whether the effects of DE exposure on systemic vascular endothelial function were caused by UFPs or by the gaseous component of DE; 16 healthy volunteers inhaled 4 different atmospheres: diluted DE (particle concentration of 300 μg/m^3), laboratory generated carbon UFPs (< 100 nm, 4×10^6 particles/cm^3), filtered DE, or filtered air. After each exposure, forearm blood flow was measured in response to infusion of vasoconstrictors and vasodilators; Figure 21 provides illustrative results for the vasodilator, acetylcholine. The impairment of vascular responsiveness with exposure to whole DE that had been observed in an earlier study (Mills et al. 2005) was confirmed (panel A). However, neither filtered exhaust (panel B) nor pure carbon UFPs (results not shown, but were the same as for filtered exhaust) affected endothelial function measured by forearm blood flow. These experiments indicate that the particulate component of DE was responsible for the vascular effects, and that carbon UFPs alone do not reproduce the effect. Thus, it appears that particle size is not the only factor determining the vascular effects of DE. The findings do not exclude the possibility that some aspect of the gas–particle mixture is responsible.

Real-World Ambient Air Studies Brauner and colleagues (2008) performed an intervention study in 21 nonsmoking couples, ranging in age from 60 to 75 years, in their homes in Copenhagen, Denmark. Investigators installed high-efficiency particle filters in their homes, and the study consisted of consecutive 48-hour periods living with either filtered or unfiltered indoor air. The exposures were double-blinded and randomized, and monitoring included

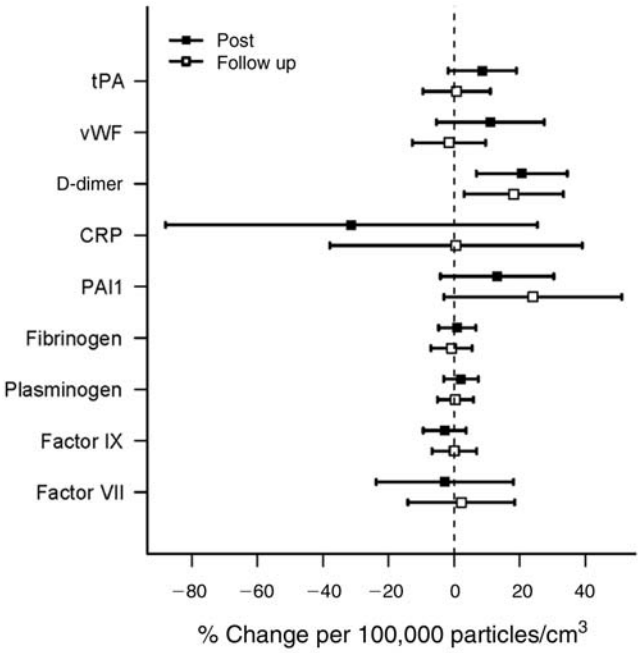

Figure 20. Effects of concentrated quasi-ultrafine particles (< $PM_{0.16\ \mu m}$) on D-dimer in blood and other markers of coagulation. (Source: Samet et al. 2009, reprinted with permission of the American Thoracic Society.)

particle counts and fine and coarse mass concentrations. Filtering reduced mean particle counts from 10,016 to 3,206 particles/cm^3 and reduced mean $PM_{2.5}$ mass from 12.6 to 4.7 μg/m^3. Microvascular function, measured by digital peripheral artery tone after arm ischemia, improved by 8.1% during air filtration. However, this effect was more strongly related to the $PM_{2.5}$ mass concentration than to particle number, suggesting that reductions in UFPs were not the driving influence in improving vascular function.

As part of the study discussed earlier, Rundell and colleagues (2007) also assessed systemic vascular effects of exercise in outdoor environments with high versus low ambient particle counts. Higher particle count exposures were associated with markedly reduced systemic vascular function (measured by reduced flow-mediated dilatation of the forearm) and reduced reperfusion of small vessels of the forearm (measured by near-infrared spectrometry).

A recent study of cyclists in Ottawa, Canada found suggestive associations of total NC with reduced HRV parameters within four hours of the start of cycling, although some results were sensitive to outliers; select associations with other pollutants (e.g., BC, NO_2, and O_3) were also observed with HRV endpoints (Weichenthal et al. 2011).

Laumbach and colleagues (2010) piloted a protocol for assessing the effects of car commuting on HRV measures. The authors recruited 21 subjects with type 2 diabetes to participate in 90- to 110-minute car rides on a busy

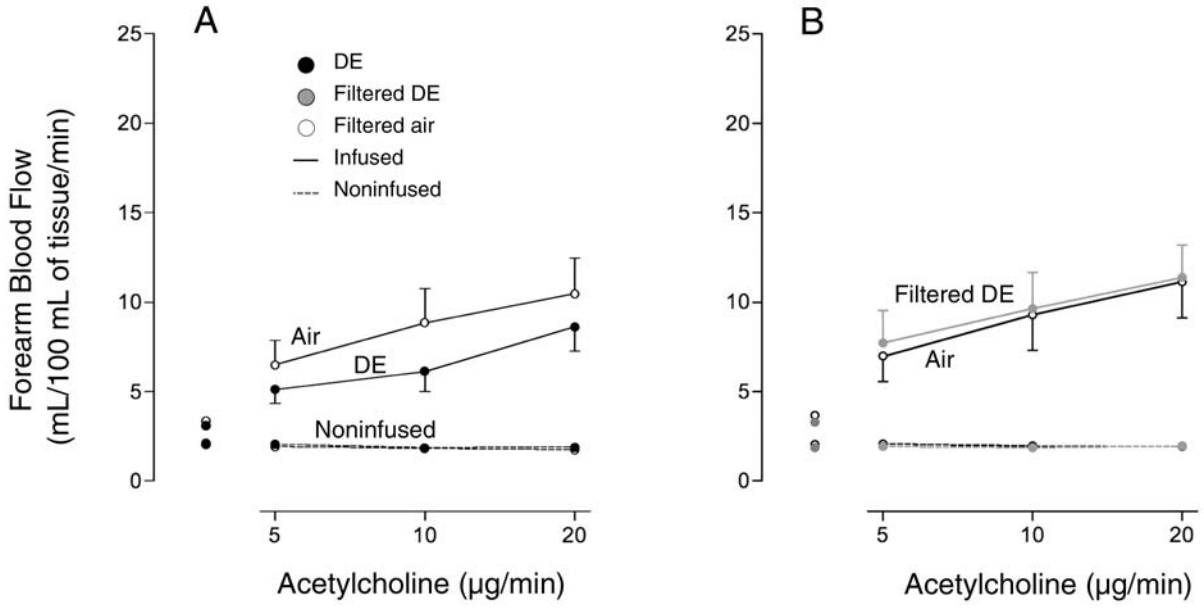

Figure 21. Endothelial function and exposure to diesel exhaust particulates after acetylcholine infusion. Forearm blood flow was measured in healthy subjects 6–8 hours after exposure to DE, filtered DE, or filtered air — either during acetylcholine infusion or without any infusion. Significant dose-dependent increases in blood flow were observed with infusion ($P < 0.0001$) versus without infusion. This effect was significantly attenuated with exposure to DE (panel A; $P = 0.008$), but not with filtered DE (panel B; $P < 0.05$). Results using carbon UFP were similar to those for filtered DE (not shown). (Source: Mills et al. 2011b, by permission of Oxford University Press.)

highway in New Jersey. Changes in HRV parameters (e.g., reduced high-frequency HRV) relative to pre-ride levels were observed post-ride and on the next day, and while not statistically significant, the authors linked these with in-vehicle pollutant concentrations (total NC, $PM_{2.5}$, CO, NO_2). Potential confounding by perceived stress and anxiety was considered in this study using a stress questionnaire that was administered at four time points during each sampling session. Observed results were independent of stress or anxiety in sensitivity analyses that excluded subjects with high stress or anxiety scores. Noise levels, however, were not measured in this study.

Summary of Human Cardiovascular Responses As noted for respiratory responses, there are a small number of studies examining cardiovascular endpoints, with differing approaches and a range of findings. Human exposure studies to carbon UFPs in Rochester, New York, suggested small, transient effects on both pulmonary and systemic vascular function. However, the study by Mills and colleagues (2011b) examining the components of DE found that inhalation of carbon UFPs did not reproduce the vascular effects of whole DE. Indoor air filtration in the homes of older subjects improved microvascular function, but the effect was more strongly related to PM mass than to particle number, implicating the larger particles in the indoor air mix.

With regard to cardiac ECG monitoring, both the Rochester and Chapel Hill studies, using carbon UFPs and concentrated UFPs respectively, suggested effects on cardiac repolarization and increases in high-frequency and low-frequency power, without substantial effects on time-domain variables of HRV. However, the study by Gong and colleagues (2003, 2008) in Southern California showed reductions, rather than increases, in low frequency power. Thus, the effects of UFP inhalation on cardiac autonomic function remain unclear.

There is evidence that carbon UFP exposure activates platelets in people with diabetes, and that concentrated ambient UFPs activate coagulation, an effect not seen with concentrated fine and coarse particles. However these studies require confirmation.

Thus, there is evidence in some studies for UFP effects on vascular function, HRV, cardiac repolarization, and coagulation, all findings that support adverse cardiovascular influences of exposures to UFPs, especially for people with underlying heart or vascular disease. However, there are

inconsistencies among studies. There remains insufficient evidence from human studies for definitive conclusions about cardiovascular effects of inhalation exposure to UFPs.

Other Responses One study (Vinzents et al. 2005) looked at measures of oxidative and mutagenic activity (level of DNA purine oxidation and strand breaks) in 15 healthy nonsmoking subjects who bicycled in traffic on five occasions and in the laboratory on one occasion, with personal monitoring of total particle number counts. Cumulative outdoor and indoor exposures to UFPs were each independent predictors of the level of DNA purine oxidation, but not of strand breaks. Other outdoor pollutants, including PM_{10}, NO_x, CO, and urban background UFP concentrations were not significant predictors of oxidative or mutagenic activity.

Summary and Conclusions for Experimental Studies

UFPs have unique physical properties that determine their deposition and disposition in the respiratory tract. These characteristics indicate that, with repeated or prolonged exposures, UFPs have a greater potential than fine particles for retention in the lung. Studies in animals have suggested that UFPs can enter the blood and move beyond the lung, although the extent to which this happens in humans remains unknown. These properties indicate a potential for adverse effects in the lung and in other organs.

Animal studies indicate that inhalation of UFPs at concentrations relevant to ambient air does not cause substantial lung inflammation. However, UFPs have been shown to enhance responses to allergens in allergen-sensitized and challenged animals, increase the progression of atherosclerosis in susceptible animal models, and influence the autonomic control of the heart. UFPs have been shown to translocate from the nose to the brain via the olfactory nerve, and there is evidence for increased inflammatory markers in the brain of exposed rodents.

Human chamber studies with exposure to carbon UFPs and to concentrated ambient UFPs have been fairly consistent in finding no effects on lung function or airway inflammation. Some chamber studies found UFP effects on vascular function, cardiac repolarization, HRV, and blood coagulation, suggesting that UFPs may have effects outside the lung in the absence of lung inflammation. Other chamber studies, however, have shown conflicting data. One real-world study showed declines in lung function and increased airway inflammatory markers in subjects with asthma.

Both animal and human studies provide evidence for respiratory and cardiac effects, and animal exposure studies suggest the possibility of effects on the brain. However, the ability to draw definitive conclusions is limited by the absence of long-term animal exposure studies and by somewhat inconsistent findings in human clinical studies. Human clinical exposure studies remain limited by the technology available to generate exposures relevant to ambient UFPs: laboratory-generated particles are not completely representative of ambient UFPs, and concentrator studies are limited to the larger, quasi-UFPs.

Real-world ambient exposure studies arguably offer the most realistic exposures to ambient UFPs, and some adverse respiratory and cardiovascular responses associated with those exposures have been observed. However, such studies always involve exposures to complex mixtures, and even with appropriate study designs, with current statistical methods it is challenging to separate completely the effects of UFPs from those of other pollutants. The results of these studies contribute to the traffic-related air pollution and health literature by suggesting high exposure to traffic-related pollutants (and associated factors, such as noise and stress or anxiety) during commuting may be relevant for human health.

Collectively, the studies reviewed in this chapter do not provide strong evidence that short-term exposures to UFPs have effects that are dramatically different from those of larger particles; the effects of long-term, repeated experimental exposures to UFPs are unknown.

CHAPTER 4. Do UFPs Affect Human Health at Environmental Concentrations? What Is the Evidence from Epidemiologic Studies?

In the previous chapters, we have explored the sources and environments which could result in human exposure to UFPs, and the evidence for possible health effects deriving from controlled animal and human exposure studies. In this section, we examine the evidence base from epidemiologic studies that attempt to address directly the most central question of this issue of HEI Perspectives: Does ambient UFP exposure have an adverse effect on human health?

Our evaluation of the literature in this chapter considers this question from two angles: 1) an evaluation of the evidence for specific endpoints, with an assessment of the consistency and coherence of observed associations, and 2) an evaluation of the evidence with respect to key study design and data issues, including UFP measurement, exposure assignment approaches, and consideration of potential copollutant confounding. In doing so, we attempt to address the overarching question as to whether any observed UFP effects are independent of those

observed for other particle sizes or for other combustion- or traffic-related pollutants.

The intent of this document is to provide a broad survey of the state of the science on UFPs by describing the nature and scope of the current body of evidence. This survey summarizes the human health outcomes, exposure assessment approaches, and the ways that the studies account for the complex multipollutant exposure environment that often accompanies UFPs. In this chapter, we do not give an intensive quantitative meta-analysis or a more systematic, in-depth literature review. Instead, we will use this survey of studies to identify areas of investigation that are needed to more fully understand the specific effects of UFPs on human health, if any, and to guide recommendations for future exploration of human health and UFP exposure.

EVIDENCE BASE

We searched for all articles published through December 2011 that examined associations between UFPs and health using online databases (Web of Science and PubMed) and personal article collections. The U.S. EPA's 2009 Integrated Science Assessment for Particulate Matter (PM ISA; U.S. EPA 2009) was also used as a source for relevant articles.

We included for consideration any epidemiologic (i.e., observational) study utilizing one or more relevant UFP metrics (i.e., number, mass, or surface area concentrations) as the measure of exposure in the health model. For number concentration, while we focused on articles that assessed UFP NC for particles < 100 nm, we included some articles that measured total NC, where the size range is unspecified or varies between 3 and 1000 nm (but where the study authors expect that the total number of particles will be dominated by the number of particles in the < 100 nm range). Studies that measured only particles > 0.3 μm were excluded, as were studies with no particle count or particle size measurements. For example, studies of traffic using only distance to roadway measures or pollutant measures that were not specific to UFPs, such as $PM_{2.5}$ EC, were excluded. We also focused on studies involving exposure to ambient UFPs or ambient UFP surrogates and therefore excluded articles focused on nanotechnology and exposures to workplace engineered nanoparticles.

The following groups of articles were identified: 1) 8 relevant reviews published in the years 2009–2011; 2) an expert elicitation conducted to assess causality and concentration–response functions for UFPs and health; and 3) over 75 articles presenting primary research on the relevant UFP metrics. Overall findings from the first two groups of articles, including the 2009 PM ISA (U.S. EPA 2009), were used as a starting point for examining whether ambient UFPs affect human health. Studies published since the 2009 PM ISA were evaluated together with prior evidence to determine whether recent findings further our understanding of whether ambient UFPs adversely affect human health.

PREVIOUS REVIEWS

The 2009 PM ISA reviewed over 40 primary research articles that examined the effects of UFPs on health (published in years 2000–2009) (U.S. EPA 2009). This report found that in a limited number of epidemiologic studies the investigators observed associations of UFPs and acute respiratory effects, such as respiratory symptoms in infants (Andersen et al. 2008a) and in adults with asthma (Von Klot et al. 2002) as well as hospitalizations and emergency department visits for asthma and pneumonia (Andersen et al. 2008b; Halonen et al. 2008). However, associations were not observed in all studies, such as in a study in Atlanta of emergency department visits and high UFP concentrations (38,000/cm^3) (Peel et al. 2005). Similarly for cardiovascular outcomes, the 2009 PM ISA reviewed a small number of epidemiologic studies and found inconsistent evidence for an association between UFPs and CVD hospital admissions, although some positive associations for subclinical cardiovascular measures (i.e., arrhythmias and supraventricular beats) were cited. Taken together with toxicologic findings, the 2009 PM ISA concluded that evidence of a causal relationship between short-term UFP exposure and respiratory or cardiovascular effects is suggestive. Evidence of causal relationships between UFP exposure and other acute outcomes (e.g., mortality and central nervous system effects) and chronic outcomes (e.g., cardiovascular and respiratory effects, reproductive and developmental effects, cancer, genotoxicity, and mutagenicity) was deemed inadequate.

An expert elicitation was also recently conducted to specifically assess the likelihood of causal relationships (separately and independently from effects of coarser particle fractions or other components of the air pollution mix) and the likelihood of potential causal pathways for cardiac events (Knol et al. 2009). A panel of twelve European experts (epidemiologists, toxicologists, and clinicians) rated the causality of health effects of short-term UFP exposure as medium to very high for all-natural-cause mortality, low to high for cardiovascular and respiratory hospital admissions, very low to medium for cough, low to high for aggravation of symptoms in asthma patients, and low to very high for decrements in lung function. The experts rated the likelihood of a causal relationship between long-term UFP exposure and health effects as ranging from low to very high, with most evidence deemed

as indirect. Of the causal pathways for cardiac events evaluated, the pathway involving respiratory inflammation and subsequent thrombotic effects was rated as most likely; the pathway with the lowest ratings involved translocation of particles affecting the autonomic nervous system and affecting HR, HRV, and arrhythmia endpoints. Lower ratings by experts were motivated by issues such as reliance of studies on limited UFP data, exposure misclassification, lack of evidence for the independent effects of UFPs, lack of correction for publication bias, and lack of data on long-term UFP exposures.

These and other review articles struck similar themes regarding the limitations of available epidemiologic evidence for the effect of ambient UFPs on human health:

1. The reviews each noted an inadequate base of evidence with which to assess different facets of the UFP health effects field: that is, the lack of coherent studies assessing specific disease, organ or system-based endpoints that would lead to specific mechanistic hypotheses (Araujo and Nel 2009; Lotti et al. 2009; U.S. EPA 2009), limited knowledge of the effect of exposures in specific microenvironments such as those related to commuting (Knibbs et al. 2011) or in school environments (Mejia et al. 2011), and the lack of studies assessing the effects of long-term exposures (U.S. EPA 2009; Knol et al. 2009; Hoek et al. 2010).
2. Several of the reviews addressed the difficulties in assessing UFP effects in epidemiologic settings. UFP monitoring data are scarce. Also, assigning UFP exposures using data from single ambient monitoring sites results in a high likelihood of exposure misclassification due to the high spatial variability of UFP concentrations (Fanning et al. 2009; U.S. EPA 2009; Terzano et al. 2010). In the expert elicitation (Hoek et al. 2010), exposure misclassification was identified as a high source of uncertainty in epidemiologic investigations into UFPs.
3. High covariation of UFPs with other combustion-related pollutants, such as CO and NO_2, makes it difficult to disentangle the independent effects of UFPs from these pollutants or the traffic-related mix in general (U.S. EPA 2009; Knol et al. 2009).

For this document, we evaluated the primary research articles based on their ability to provide evidence that would help address these limitations.

LONG-TERM EFFECTS

There have been no studies that have examined long-term UFP exposure and health with the kinds of retrospective or prospective cohort study designs that have played influential roles in characterizing the chronic cardiorespiratory effects of PM_{10} and $PM_{2.5}$. The absence of such studies is directly related to the limited monitoring of UFPs over time and with insufficient spatial resolution to identify the spatial contrasts in population exposures on which long-term studies typically rely.

Instead, investigators have attempted to use cross-sectional study designs that assess the prevalence of chronic diseases in relation to concentrations of UFPs in different locations within a particular period (Lwebuga-Mukasa et al. 2005; Cahill et al. 2011; Kim et al. 2011). For example, Kim and colleagues (2011) reported results of a survey of over 1900 schoolchildren from 12 schools in Korea for which indoor and outdoor school environmental measurements were conducted over a 7-day period in winter 2004. This study found associations of wheeze and asthma (in the previous year) with a number of home environment factors, such as water damage, visible mold growth, and indoor dampness. Among the outdoor measurements, associations of wheeze with NO_2 and current asthma with total NC were observed. Lwebuga-Mukasa and colleagues (2005) examined total NC in relation to asthma prevalence among Buffalo, New York, neighborhoods using a cross-sectional survey of over 1600 households. The authors found that total NC was highest in neighborhoods downwind of the Peace Bridge Complex, a commercial truck traffic corridor on Buffalo's west side; these neighborhoods also had the highest asthma prevalence in the study.

The cross-sectional design of these studies is a limitation. With no information on long-term personal exposures, it is not possible to attribute exposures to disease onset or progression. Nor is it possible to tease apart the potential effects of particle number from those of other potential causal factors (i.e., confounders) for asthma that may covary spatially with particle number. For example, in the article by Lwebuga-Mukasa and colleagues (2005), NCs were examined as one of several potential factors contributing to asthma prevalence or exacerbation; traffic-related pollution, distance to source, home environmental conditions, and socioeconomic differences among neighborhoods in this region.

SHORT-TERM EFFECTS

Studies of the health effects associated with short-term exposures (e.g., hourly or daily) are easier to conduct and are far more common. We reviewed over 75 articles and reports for studies assessing the short-term health effects of ambient UFPs, including over 25 articles from the 2009–2012 period that were not included in the 2009 PM ISA (U.S. EPA 2009). In this section the articles reviewed presented UFP exposure that was represented by number

concentration data. A small number of studies that evaluated UFP mass concentration data are considered separately in a later section, *Epidemiologic Studies Using Measures of UFP Mass*.

Figure 22 provides an overview of the geographic distribution of the studies reviewed. It indicates that the large majority of the short-term studies reviewed to date have been conducted in Europe and that several European cities (e.g., Erfurt and Copenhagen) have been studied repeatedly in the literature. Moreover, European research activity on UFPs is concentrated primarily in western European countries. More details on the study design features of the primary short-term research studies reviewed, organized by the health endpoints and geographic location, are provided in Appendix Table B.1. The table includes more specificity on the UFP measurement methods and metrics used in the study (i.e., sized-differentiated number concentrations) than provided in this chapter. For simplicity, we have

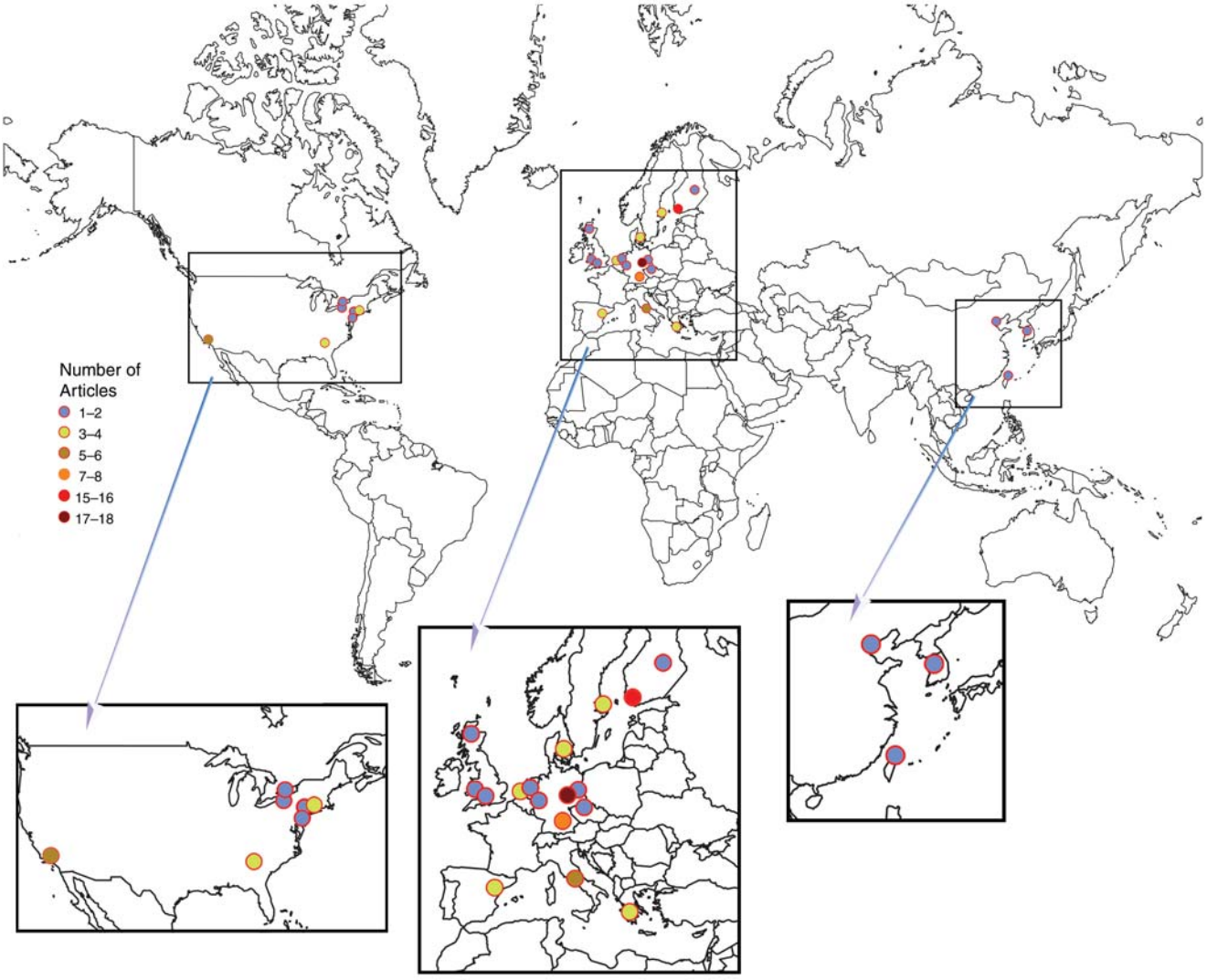

Figure 22. Geographic locations of epidemiologic investigations of the short-term exposures to UFPs discussed in this chapter. A number of populations in a given location have been the subject of multiple articles.

reported results for total NC when that was the only measure of UFP provided, and for UFP NC, representing the NC size fraction closest to the definition used in this document (e.g., NC < 100 nm).

Mortality

Several population-based studies examining the association between short-term exposure to total or UFP NC and mortality that were conducted over the past 10 years compared ambient central site particle measurements to various mortality outcomes (e.g., all-natural-cause, respiratory, cardiovascular, or stroke mortality) using time-series or case–crossover approaches (Appendix Table B.1). Most of these studies considered various particle and gaseous pollutant metrics in association with mortality. In general, associations of NC and mortality were not consistently observed across the studies. Strong (significant) associations with NC were noted in the studies conducted in Erfurt, London, Rome, and Beijing and weak or no associations were observed in studies conducted in Helsinki and Prague. Closer evaluation of study designs and exposure characteristics in different study locations would be necessary to better understand sources of variability in the findings. The strongest associations with NC reported in most studies were largely for cardiovascular causes of death. Breitner and colleagues (2011) assessed associations of various particle size metrics (number, mass, and surface area concentrations) and cause-specific cardiovascular deaths in Beijing and reported that the strongest associations were between all cardiovascular and ischemic heart disease mortality and UFP NC, with weaker or null associations with larger size fractions and with other UFP metrics (see Figure 23).

In general, however, differences in the specific mortality outcomes and in the lag structure of the associations examined in the various studies make it difficult to fully assess the consistency of the results. In Erfurt 1995–2001, for example, robust associations between UFP NC and total mortality and a combined cardiovascular and respiratory mortality grouping were found for a 4-day lag (other lags in the 0–5 day range were not significant) (Stölzel et al. 2007) as well as for longer averaging periods (i.e., 6- and 15-day polynomial distributed lag models) (Breitner et al. 2009). In contrast, among the other studies that found associations with NC, strongest associations were observed for shorter lags (lag 0, 1, or 2) (Forastiere et al. 2005; Kettunen et al. 2007; Atkinson et al. 2010; Breitner et al. 2011).

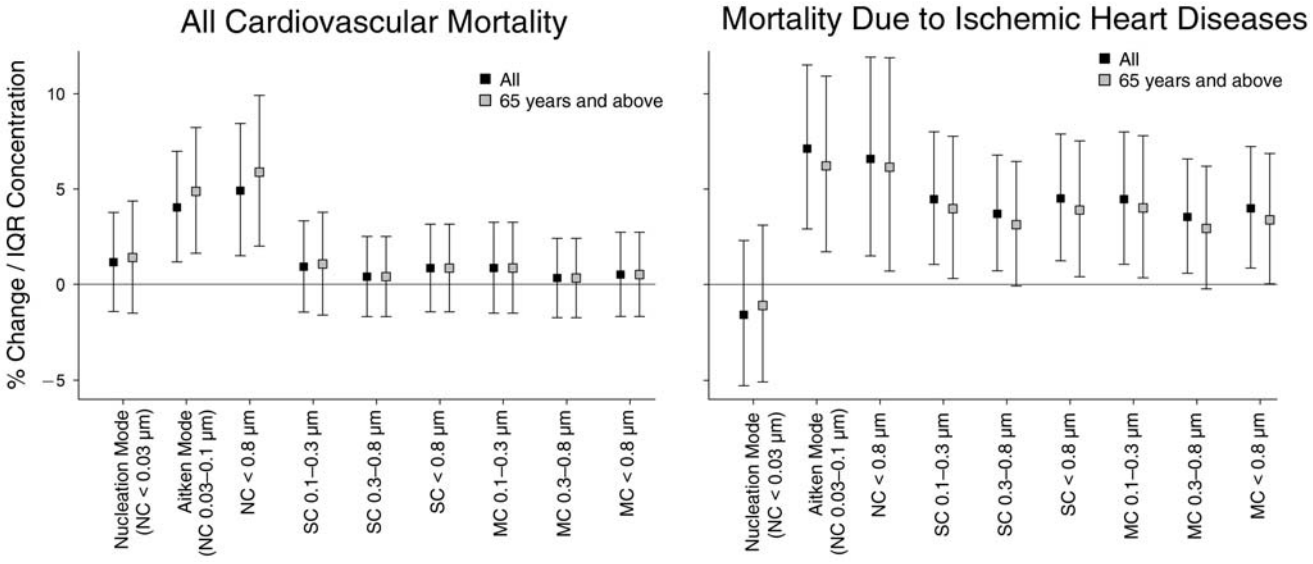

Figure 23. Percentage change (and 95% confidence interval) in cause- and age-specific cardiovascular mortality per an interquartile increase in particle metrics in Beijing, from March 2004 to August 2005. The investigators measured particle number concentrations (NC) which they then converted into surface area concentrations (SC) and mass concentrations (MC) for the specific size ranges indicated (using assumptions found in the published paper). The interquartile ranges for the different metrics were: nucleation mode (NC < 0.03 µm), 10,203/cm^3; Aitken mode (NC 0.03–0.1 µm), 6,250/cm^3; NC < 0.8 µm, 13,790/cm^3; SC 0.1–0.3 µm, 469.9 µm^2/cm^3; SC 0.3–0.8, 486.7 µm^2/cm^3; SC < 0.8 µm, 973.7 µm^2/cm^3; MC 0.1–0.3 µm, 24.0 µg/m^3; MC 0.3–0.8 µm, 57.9 µg/m^3; and MC < 0.8 µm, 81.8 µg/m^3. (Source: Breitner et al. 2011, Figure 2, reprinted with permission from Elsevier.)

Moderate to high correlations between UFP NC and mobile-source related gases (CO, NO_2) have also made it difficult to implicate UFPs, as opposed to more general mobile-source emissions, in observed associations with health endpoints (U.S. EPA 2009). Indeed, in most papers, authors implicate combustion sources, as opposed to UFPs specifically, as affecting mortality. For example, while the authors did not specifically assess the effects of traffic-related gases or particle components, Atkinson and colleagues (2010) indicated that NC in London is largely influenced by nucleation-mode particles from diesel traffic that have a high OC component. In their analysis, NO_x data were used to apportion PM measures into primary and nonprimary components; the authors observed a high correlation (r = 0.77) between total NC and primary PM_{10}. In Rome, observed associations were strong for both total NC and CO, with a high correlation (r = 0.89) observed between these pollutants (Forastiere et al. 2005). In Helsinki, associations were suggestive for UFP NC and CO in the warm, but not the cold, season (UFP NC–CO warm season correlation, r = 0.39) (Kettunen et al. 2007). Breitner and colleagues (2011) did not include CO and NO_x in the Beijing analysis, but the authors indicated that UFP NC (30–100 nm) was highly influenced by local traffic emissions.

Some studies have investigated multipollutant models of UFP NC with other particle or gaseous copollutants as a means of controlling for potential copollutant confounding. In Erfurt, associations of UFP NC and total mortality for the 1995–2001 period appeared to be independent of those for mobile-source–related gases (CO, NO, NO_2) (i.e., in two-pollutant models, the effects of UFP NC adjusted for individual gases were even slightly higher than those for UFP NC alone, as indicated in Figure 24, but did not change the interpretation of the UFP NC results); two-pollutant models of UFP NC and mass concentration metrics (i.e., $PM_{2.5}$ and PM_{10}, which showed no association with mortality in this study) were not reported (Stölzel et al. 2007). In Erfurt, daily mean UFP NC were moderately correlated with daily mean CO (r = 0.57), NO_2 (r = 0.65), $PM_{2.5}$ (r = 0.51), and PM_{10} (r = 0.56). In Beijing, associations of UFP NC and mortality were unchanged in models that included other NC or mass concentration metrics (e.g., nucleation mode NC in the 10–30 nm size range and accumulation mode mass concentration in the 100–800 nm size range); this study however did not consider CO or NO_2 (Breitner et al. 2011).

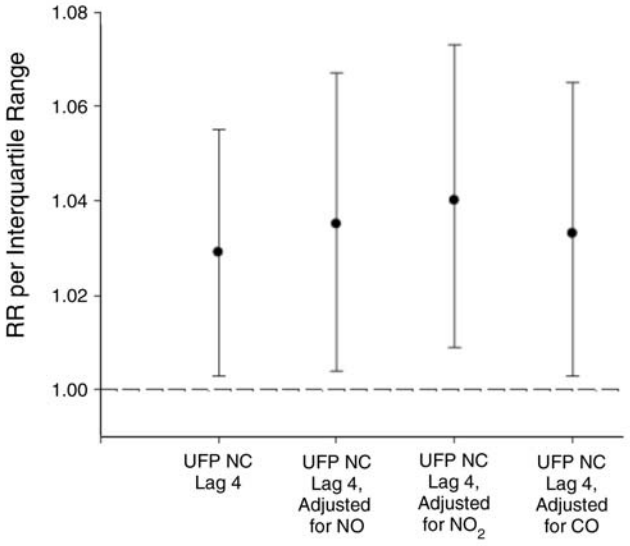

Figure 24. Relative risk of mortality per interquartile range of UFP NC (NC 0.01–0.1µm), adjusted for gaseous pollutants in two-pollutant models. Erfurt, Germany, September 1995 to August 2001. These results indicate that accounting for the presence of gaseous copollutants did not substantially change the UFP NC relative risks of mortality 4 days post exposure (lag 4) in this study. Significant associations of UFP NC with mortality were found at this lag but not generally with shorter lags in this study (Source: Stölzel et al. 2007, Figure 3, reprinted with permission from Macmillan Publishers Ltd: Journal of Exposure Science and Environmental Epidemiology.)

Cardiorespiratory Acute Morbidity

Population-based studies assessing associations of NC and acute morbidity (using data on emergency department visits, hospital admissions, physicians' visits, or emergency service calls) have mainly been conducted in Europe (Appendix Table B.1). Similar to studies assessing mortality, daily ambient central site particle measurements were used in these studies in relation to measures of morbidity using time-series or case-crossover approaches. Most of these studies considered a variety of particle and gaseous pollutant metrics. A number of studies have been published since the 2009 PM ISA (U.S. EPA 2009); however, it is not clear that these later studies provide additional insight into the consistency of associations for specific endpoints or clarity on the potential for UFPs to exert effects independent of copollutants.

While many studies reported associations of morbidity with NC, observed associations within studies were generally outcome dependent, age-group dependent, or both, making it difficult to assess consistency across studies. For example, Andersen and colleagues (2008b) observed significant associations of 5-day mean total NC (6–700 nm) and respiratory disease admissions, but not CVD admissions, in subjects 65 years or older in Copenhagen; associations with total NC were nonsignificant for pediatric asthma in this analysis and remained nonsignificant and weaker than associations with

other PM and gaseous pollutants in a follow-up study in Copenhagen that added four additional years of data (Iskandar et al. 2012). In a study in Helsinki, investigators also observed associations of 5-day mean UFP NC (30–100 nm) with pneumonia and a combination of other respiratory disease admissions in the population 65 years or older, but they found no associations with asthma or COPD admissions (Halonen et al. 2009) or for emergency department visits (Halonen et al. 2008) in this age group. Pediatric asthma emergency department visits, however, were associated with UFP NC (30–100 nm) at 3–5 day lags in Helsinki (Halonen et al. 2008). Differing study period lengths, daily outcome counts, and modeling choices also likely affect the pattern of observed associations by study and preclude attempts at meta-analysis.

Moreover, for most studies in which UFP effects were observed, associations for other particle measures (PM mass concentration and/or accumulation mode NC) or gaseous copollutants were also reported. Observed NC effects remained after controlling for PM_{10} or $PM_{2.5}$ in several studies (Von Klot et al. 2005; Lanki et al. 2006; Belleudi et al. 2010), however, they were diminished in other studies (Andersen et al. 2008b). Only two studies found independent associations with NC after controlling for CO, NO_2, or both (Andersen et al. 2010; Leitte et al. 2011). Leitte and colleagues (2011), however, indicated that NC associations were generally stronger when controlled for NO_2 than when controlled for other pollutants in two-pollutant models. In other studies, adjustment for the gases reduced the observed NC effect (Andersen et al. 2008b; Halonen et al. 2008), or the gases were not included with NC in two-pollutant models (Von Klot et al. 2005; Lanki et al. 2006; Halonen et al. 2009). In some studies, traffic-related copollutants were not considered at all, making it difficult to draw conclusions about the independence of the observed NC effects (Atkinson et al. 2010; Belleudi et al. 2010; Braniš et al. 2010; Franck et al. 2011). Overall, similar to the acute mortality studies, most authors implicate particles from traffic-related sources in the observed NC effects (Von Klot et al. 2005; Lanki et al. 2006; Andersen et al. 2008b, 2010; Halonen et al. 2008; Atkinson et al. 2010).

Respiratory Effects

In addition to population-based studies assessing mortality and morbidity outcomes, numerous panel-based and individual-level studies have been conducted that examine associations of UFPs and cardiorespiratory health endpoints. In general, specific endpoints in these studies have been chosen to reflect and support hypothesized biological mechanisms of UFPs, as described in Chapter 3. In this section, we consider observational studies investigating respiratory-related endpoints; these have included measurements of respiratory symptoms (obtained through questionnaires) and pulmonary function (obtained through spirometry).

Respiratory Symptoms Studies of respiratory symptoms (e.g., wheeze, cough, phlegm, shortness of breath) in relation to total and UFP NC have been conducted in Europe (Appendix Table B.1). Study populations have varied by age group (children, adults, older adults) and pre-existing disease (asthma, other chronic conditions). Overall, the results of these studies are inconsistent, with some studies reporting significant NC effects and some not. Similar to the previous sections, in those studies in which NC effects were observed, most of these effects were not independent from those of other particle or gaseous measurements (Peters et al. 1997; Von Klot et al. 2002; Andersen et al. 2008a).

Pulmonary Function A number of studies, also largely conducted in Europe, have assessed pulmonary function in relation to total and UFP NC (Appendix Table B.1). The results of these studies have again been inconsistent, with a majority of studies observing few effects of UFP NC specifically. Many of these studies were conducted in the 1990s and considered ambient fixed-site particle measurements in relation to subjects' daily measurements of PEF, a measure of airflow obstruction during exhalation.

One recent study adds to the literature in terms of the exposure assessment approach utilized, with effects estimated using several different exposure metrics. De Hartog and colleagues (2010) conducted a multicity study in four European cities (Helsinki, Finland; Athens, Greece; Amsterdam, the Netherlands; Birmingham, UK) with 135 subjects with mild to moderate asthma or COPD. This study was specifically designed to assess the effect of exposure assignment approaches on observed epidemiologic results. The authors compared associations of total NC and lung function among different exposure metrics (ambient central site, home outdoor, and home indoor). Overall, no consistent associations were observed for any particle metric with lung function, even after various modeling specifications and controlling for medications use and lung function measurement time-of-day, or restricting the analysis to people with asthma. Furthermore, associations were not stronger when exposures measured in the subjects' homes were used in the analyses. The authors cite several potential explanations for the null findings in this study; for example, stated limitations of this study were the *1-week design* (each subject monitored over just a 1-week period), which did not allow for assessment of lags longer than 2 days for the home-based metrics, and that

94% of subjects used respiratory medication. However, the detailed exposure characterization in this study mostly rules out exposure measurement error as a contributing factor to the null findings. Ultimately, the observed results could also be due to lack of a true association between UFPs and lung function.

Allergy and Atopy While allergy is often considered in the context of respiratory responses, Song and colleagues (2011) recently conducted a panel study in Incheon to examine associations of UFPs and other pollutants, with atopic symptoms in 41 elementary school children (ages 8–12) with atopic dermatitis. The authors reported a strong UFP NC effect that appeared to be independent of other pollutants: 1-day lagged UFP NC was associated with skin itching, but other pollutants were not (PM_1, $PM_{2.5}$, PM_{10}, NO_2, SO_2, and O_3). Associations remained in two-pollutant models with PM mass metrics. A limitation of this study was that PM measurements were conducted on the roof of the school while the gaseous pollutants were collected at an ambient fixed site located two kilometers from the school. Because the UFPs were measured closer to the school, it is possible that there was less exposure misclassification for UFPs compared with the gases in this study. Distance from the collection site may be a reason for the lack of effects observed with the gaseous pollutants.

Cardiovascular Effects

In addition to respiratory endpoints, panel-based and individual-level studies have considered a number of cardiovascular endpoints, such as ECG-related outcomes (e.g., HRV, arrhythmias, ischemia), vascular reactivity, BP, and soluble blood (and urinary) markers of systemic inflammation, coagulation, and oxidative stress. These endpoints broadly relate to autonomic nervous system, inflammatory, and oxidative stress-related pathways hypothesized as routes of action for ultrafine as well as for other particle size fractions.

Heart-Rate Variability A number of studies were found that examined associations of total NC or UFP NC with HRV, including time-domain (e.g., SDNN, r-MSSD) and frequency-domain (e.g., low-frequency [LF], high-frequency [HF], LF:HF ratio) endpoints obtained from analysis of ECG measurements (Appendix Table B.1). These studies were conducted in cities across Europe, North America, and Asia and were largely repeated-measures panel studies in which multiple measurements were taken in the same individual over time. The one exception was an analysis conducted as part of the Normative Aging Study cohort for years 2000–2003, which provided outcome data for one sampling session per subject throughout the study period (Park et al. 2005).

These six studies considered a range of different exposure measurements. Five studies used ambient fixed-site NC measurements (Park et al. 2005; Timonen et al. 2006; Barclay et al. 2009; Schneider et al. 2010; Rich et al. 2012). One study incorporated personal total NC (20–1000 nm range) monitoring (Chan et al. 2004), and the study by Barclay and colleagues (2009) estimated personal UFP NC exposures based on ambient fixed-site measurements.

Associations of HRV effects with NC were not observed consistently: associations were observed in only three of the six studies (Chan et al. 2004; Timonen et al. 2006; Rich et al. 2012). A variety of factors may have contributed to the positive associations observed in these studies, such as the reduced uncertainty in exposure assignment due to the personal exposure characterization by Chan and colleagues (2004) and the relatively high statistical power of the multicity study design (the ULTRA study) by Timonen and colleagues (2006). It should be noted, however, that these studies also reported similar effects associated with exposures to other particle size fractions and gases.

Arrhythmia and Related Endpoints Studies of arrhythmias and total and UFP NC have also largely been conducted in Europe, with studies in Aberdeen, Augsburg, Erfurt, and London and one study conducted in the United States, in Boston (Appendix Table B.1). These studies have considered arrhythmias detected in individuals with implanted cardioverter defibrillators (ICDs), as well as arrhythmias detected in panel study subjects through analysis of ECG recordings.

The ICD studies focus on serious ventricular arrhythmias (e.g., ventricular tachycardia, ventricular fibrillation) that ICDs are designed to detect and treat (such as with pacing or shock). In a follow-up study of ICD patients living in eastern Massachusetts, Dockery and colleagues (2005a,b) found associations between ventricular arrhythmias and 2-day mean $PM_{2.5}$, BC, CO, NO_2, and SO_2, but not for total NC or O_3, with significant associations observed only when restricting analyses to arrhythmias occurring within three days of a previous arrhythmia. It should be noted that NC measurements were only available for one third of the study period; consequently, the null associations with NC may have been a function of limited data (and lower statistical power). The authors implicated traffic pollution in this study. In London, traffic-related pollutants (total NC, black smoke, CO, NO_2) assessed at 0–5 day lags were not associated with ICD-detected arrhythmias, whereas there were associations with secondary pollutants (e.g., sulfate) (Anderson et al. 2010). Null results for UFP

NC and other pollutants, assessed at 0–2 day lags, were also found in the Aberdeen panel study, in which ventricular and supraventricular arrhythmias were assessed through ECG recordings (Barclay et al. 2009). In Erfurt, Berger and colleagues (2006) observed associations of arrhythmias with 5-day mean (and shorter single-day lags of) UFP NC, but also with accumulation mode NC, $PM_{2.5}$, CO, and NO_2.

Two other panel studies conducted in Germany assessed ECG-derived measures of repolarization abnormalities (e.g., QT duration, T-wave complexity, T-wave amplitude, T-wave amplitude variability), which may be linked with the onset of arrhythmias (Henneberger et al. 2005; Yue et al. 2007; Hampel et al. 2010). The results of these studies have been mixed. No associations with total NC at 0–5 day lags were found in a panel of myocardial infarction survivors in Augsburg (Hampel et al. 2010). Henneberger and colleagues (2005) observed significant decreases in T-wave amplitude with exposures to UFP NC, accumulation mode NC, and $PM_{2.5}$ in the previous 5 and 23 hours of ECG measurements in a panel study of males with ischemic heart disease in Erfurt. Further analysis of these data suggested that local traffic-related UFP NC and diesel traffic-related source factors showed the strongest associations with repolarization parameters (Yue et al. 2007).

Ischemia Several studies have been conducted to examine the effects of particle exposure on myocardial ischemia using ST-segment changes from ECG recordings (Appendix Table B.1). These were conducted in panels of subjects with coronary artery disease in Helsinki and in Los Angeles. The two Helsinki publications focused largely on the same subject data, but assessed different lag structures: 1) Pekkanen and colleagues (2002) observed strong associations with 2-day mean UFP NC (and accumulation mode NC, PM_1, $PM_{2.5}$, CO, NO_2) and ST-segment depression during exercise tests; and 2) in an assessment of subdaily exposures, Lanki and colleagues (2008) observed associations with 1- to 4-hour lagged $PM_{2.5}$, but not with UFP NC. In Los Angeles, Delfino and colleagues (2011) found ST-segment depression associated with home outdoor traffic-related pollutant measures (including $PM_{2.5}$, $PM_{0.25}$, BC, primary OC, CO, NO_2) at various lags (including 1-hr, 8-hr, and 1–3 day means), but not for total NC ($r = 0.36$ between total NC and $PM_{0.25}$) in a panel of older subjects living in a retirement community.

Vascular Reactivity Only two studies have considered vascular reactivity in relation to exposure to particle count measures (Appendix Table B.1), and both studies have found little association with NC. In a panel of subjects with diabetes or at risk for diabetes in Boston, O'Neill and colleagues (2005) examined associations of ambient particle concentrations and two measures of vascular reactivity: non–endothelium-dependent nitroglycerin-mediated reactivity and endothelium-dependent flow-mediated reactivity. Total NC was associated with nonsignificant decreases in both measures, while other particle metrics ($PM_{2.5}$, BC, and sulfate) showed significant inverse associations. Dales and colleagues conducted a *bus stop study* in a panel of healthy subjects who were asked to sit at one of two bus stops in Ottawa, Canada, for two hours (Dales et al. 2007). Associations between $PM_{2.5}$ and flow-mediated dilatation were observed, but not with NO_2, total NC (≤ 1 µm), or traffic density.

Blood Pressure A limited number of studies have considered changes in HR and BP, which both reflect changes in autonomic tone, in relation to NC measures. These studies have been conducted in Europe as part of the multicity ULTRA study (Amsterdam, Helsinki, and Erfurt), in Los Angeles, in Ottawa as part of the bus stop study, and in Taipei, Taiwan (Appendix Table B.1). The results to date have been inconsistent in regard to both the direction and significance of observed associations.

In a small panel of subjects with lung function impairments, Chuang and colleagues (2005) observed positive associations between personal exposures to total NC (20–1000 nm) and HR and both systolic and diastolic BP in the 1–3 hours before the BP measurement. In contrast, in the ULTRA multicity study of adults with coronary heart disease, small but significant inverse associations between particle measures ($PM_{2.5}$, $NC_{0.01–0.1}$, and accumulation mode particles [$NC_{0.1–1.0}$]) at 0–2 day lags and systolic and diastolic BP were found in pooled analyses (Ibald-Mulli et al. 2004). In the panel study of older subjects with coronary heart disease living in retirement homes in Los Angeles, outdoor home measurements of total NC, $PM_{2.5}$, OC, BC, and gases were conducted (Delfino et al. 2010c). In overall analyses, the authors observed positive associations of systolic and diastolic BP with all particle measures, at 3–9 day mean concentrations, except for total NC. In effect modification analyses, associations with 1–8 hour lagged total NC were observed when subjects reported moderate to strenuous physical activity in the hour preceding the BP measurement. In the bus stop study, only NO_2 was associated (positively) with 2-hour bus stop exposures (Dales et al. 2007).

Soluble Markers A relatively large number of articles ($n = 16$) from eight different studies have considered total or UFP NC in relation to various blood (and urinary) markers of systemic inflammation, coagulation, and oxidative stress, pathways that are linked with processes of CVD and atherosclerosis (Appendix Table B.1). The large range

of specific markers examined across these studies makes it difficult to fully assess the consistency of effects. However, there have been a handful of common markers used across studies, including C-reactive protein (CRP) and interleukin-6 (IL-6) as markers of systemic inflammation, and fibrinogen as a marker of coagulation.

Of the eight studies assessing endpoints for CRP, IL-6, or both, four studies observed associations with various measures of number concentration: 1) a population-based cohort study in Germany (Hertel et al. 2010); 2) a European multicity study of myocardial infarction survivors in Athens, Greece; Augsburg, Germany; Barcelona, Spain; Helsinki, Finland; Rome, Italy; and Stockholm, Sweden (as part of the AIRGENE study) (Rückerl et al. 2007a); and two well-characterized panel studies in 3) Erfurt (Rückerl et al. 2006; Rückerl et al. 2007b; Yue et al. 2007) and in 4) Los Angeles (Delfino et al. 2008, 2009). The first of these studies (Hertel et al. 2010) used a dispersion and chemical transport model to determine spatiotemporally-resolved total NC, but did not consider pollutants other than NC, $PM_{2.5}$, and PM_{10} in the analysis. The other three studies, however, in addition to observed associations with NC metrics, found associations of CRP, IL-6, or both with accumulation mode NC, CO, NO_2, or other traffic-related pollutants (such as EC in the Los Angeles study). Two-pollutant models of NC and other pollutants were not examined in these studies.

The four studies in which no significant associations were found between NC metrics and CRP or IL-6 included panel studies of: 1) adults with a previous myocardial infarction in Augsburg (Kraus et al. 2011) (although this study did find an association with plasma Lp-PLA2, a marker of vascular inflammation [Brüske et al. 2011]); 2) adult men with chronic pulmonary disease in Erfurt (Hildebrandt et al. 2009); 3) adults with stable chronic heart failure in Aberdeen (Barclay et al. 2009); and 4) adult men in the VA Normative Aging Study in Massachusetts (Zeka et al. 2006). It is difficult to generalize the differences between the positive and null studies here. However, the studies with null results for CRP were largely null not only with respect to particle number, but also with other pollutants examined. Such findings suggest that overall study design factors such as sample size or the exposure contrasts that were considered may have made detection of any underlying effect difficult.

Seven of the eight studies also assessed fibrinogen levels or other blood markers of coagulation in relation to various NC measures. The results for these endpoints have been very inconsistent; only two studies observed associations between NC and fibrinogen effects (Zeka et al. 2006; Hildebrandt et al. 2009), and studies that evaluated a range of coagulation endpoints have generally observed mixed results among the endpoints examined (Rückerl et al. 2006; Delfino et al. 2008; Hildebrandt et al. 2009).

In the Erfurt panel study, Rückerl and colleagues (2006) examined multiple blood biomarkers in a panel of coronary heart disease patients and observed associations between ambient fixed-site PM_{10}, UFP NC, accumulation mode NC, CO, and NO_2, and increased markers of inflammation (CRP) and adhesion (ICAM-1) above the 90th percentile, with the strongest associations using 2-day lagged pollutant measures; results for markers of coagulation were inconsistent (e.g., factor VII, fibrinogen, D-dimer) (Rückerl et al. 2006). In a further analysis of this panel, the authors observed associations between 0–23 hours mean UFP NC and accumulation mode NC with plasma levels of sCD40L, a marker for platelet activation (Rückerl et al. 2007b). In contrast, however, associations of 0–5 day lagged UFP NC with CRP and ICAM-1 were weak in another Erfurt panel study of male chronic pulmonary disease patients (Hildebrandt et al. 2009); in this study, associations of ambient UFP NC at 1- and 3-day lags and 5-day mean concentrations were observed for fibrinogen. The differences in findings between these two studies may be due in part to the differences in underlying health status of the patient populations examined, and may also point to limitations in the generalizability of results of small panel studies.

Delfino and colleagues have published several articles describing associations of total NC and other pollutants on blood markers and other endpoints in a panel of subjects with a history of coronary artery disease recruited from four retirement homes in the Los Angeles air basin (Delfino et al. 2008, 2009, 2010c). Overall, this study has included the most detailed health and exposure characterization of the studies published to date. The health endpoints characterized have included biomarkers of inflammation, coagulation, and oxidative stress, and the exposure characterization has included unusually detailed home outdoor and indoor measurements of UFPs, including total NC, $PM_{0.25}$, and $PM_{0.25}$ components. (See section entitled *Epidemiologic Studies Using Measures of UFP Mass* for a discussion of $PM_{0.25}$ epidemiologic results.) The results from this study have pointed to consistent associations between UFPs measured as total NC and inflammatory markers (IL-6, CRP, and sP-selectin); however, associations have also been strong for other traffic-related pollutants and components (e.g., EC, primary OC, CO, NO_2), and the authors implicate traffic emissions in their findings (Delfino et al. 2008, 2009). In contrast to the observed strong associations with the inflammatory markers, however, the results for markers of coagulation have been mixed, and the results for a measure of oxidative stress

(Cu, Zn-super oxide dismutase) have been internally inconsistent. For example, the authors observed negative and positive responder groups, with negative associations observed for certain subjects and positive associations observed for others (Delfino et al. 2008, 2009).

EXPOSURE ASSESSMENT CONSIDERATIONS

Our review of the epidemiologic literature identified several issues affecting the assessment of exposure to UFPs that are likely to have contributed to inconsistencies in observed results between studies as well as to uncertainties and limitations in assessing more specifically the contribution of UFPs to adverse health outcomes.

Copollutant Confounding

Previous reviews (e.g., U.S. EPA 2009), and many primary research articles examined as part of this evaluation, indicate that high covariation of UFPs with other combustion-related pollutants, such as CO and NO_2, makes it difficult to disentangle the independent effects of UFPs from these pollutants or the traffic-related mix in general. To illustrate this point with the currently available literature, of 42 published articles that cited any significant NC-health associations, 37 articles also noted significant effects for other particle or traffic-related pollutants and 10 articles did not consider traffic-related gases at all in the analysis (see Appendix Table B.1). Two-pollutant models were considered in some studies to assess the independence of UFP effects from other pollutants. Observed effects of NC measures did hold in two-pollutant models with other particle measures (e.g., accumulation mode NC or PM) and CO or NO_2 in some studies (8 and 3 studies, respectively). However, 5 studies reported that observed effects of NC measures did not hold in two-pollutant models with copollutants, and 23 of these studies did not consider NCs in two-pollutant models with copollutants. Multipollutant models are inherently difficult to interpret and may not be appropriate to implement with pollutants that are considered surrogates of the same source (e.g., traffic in this case). Thus, in most analyses to date, the independence of UFP effects cannot be clearly determined in the available observational study designs.

Exposure Measurement Error

Most studies assessing UFP health effects, especially the population-based studies of acute mortality and morbidity as well as many panel-based studies assessing clinical and subclinical endpoints, have utilized ambient fixed-site measurements of UFPs to represent exposures to individual study subjects. Depending on the study design and the nature of spatial and temporal variability in UFP concentrations in a study area, this approach may lead to varying degrees of error in how well individual exposures are represented (see related discussion in Chapter 2). These types of error in exposure measurement can, in turn, affect the ability of epidemiologic studies to detect associations with health outcomes.

Population-Based (Time-Series) Studies For population-based studies of short-term exposures as in daily time-series studies, exposure contrasts are temporal and assessment of short-term average population exposure for the entire study area is necessary. In these studies, ambient fixed-site monitoring data may be adequate as the measure of exposure if the temporal variability in UFP concentrations at the fixed site represents the temporal variability of concentrations over the study area. However, it is important that assessments of both spatial and temporal variability of UFPs at a range of locations within the study area be provided to assess the suitability of reliance on the fixed-site monitor for this purpose.

How well exposures are characterized for the individuals in the study can affect the strength, and in some cases the direction, of the associations that can be observed in a study. Error in exposure estimates can often bias associations between exposures and health outcomes to the null and can be one explanation for lack of observed positive associations in a study (Atkinson et al. 2010). In other cases, exposure measurement error can lead to spurious associations.

Studies indicating strong temporal correlation among monitoring sites for NC, despite differences in absolute concentrations among sites, might reassure us that the use of ambient fixed-site monitoring data in these studies is adequate for detecting underlying associations in time-series epidemiologic studies. For example, Cyrys and colleagues (2008) documented strong site-to-site temporal correlations ($r > 0.80$) for ambient UFP NC in Erfurt, Germany. However, study locations likely differ in the level of spatiotemporal variability of UFPs, and need to be evaluated directly for each study location and period. In studies that observe associations only with larger particle measures, it is possible that null findings for UFPs may be due to greater exposure error for the UFP measurements than for other size fractions (Pekkanen and Kulmala 2004).

Panel Studies Assessment of exposure in panel studies that rely on ambient fixed-site monitoring data can be more complex than for population-based studies. Ambient fixed-site measurements in these studies are less likely to accurately describe the temporal variability of exposures

for each individual, depending on their time–activity patterns and proximity to local sources, and more precise measures of exposure may be needed. For $PM_{2.5}$, results of detailed exposure assessment studies suggest that for many individuals an ambient monitoring site can adequately represent temporal variability in exposures to ambient $PM_{2.5}$ (Ebelt et al. 2000; Janssen et al. 2000; Sarnat et al. 2000, 2006b). However, there have been no studies that have directly assessed the relationship between personal exposures and ambient concentrations for UFPs.

Hoek and colleagues (2008) have approached this question in their investigation of ambient (central site), outdoor home, and indoor home concentrations of total NC, $PM_{2.5}$, PM_{10}, soot, and sulfate for over 150 homes across four European cities. In their analysis of 24-hour average data, correlations of central site to indoor concentrations were lower for total NC (r = 0.16–0.45) than for $PM_{2.5}$ (r = 0.40–0.80) and sulfate (r = 0.91–0.99). These analyses suggest that ambient fixed-site monitoring data for NCs may be less representative of individuals' exposures than they are for $PM_{2.5}$.

Addressing Potential Exposure Error To overcome some of the concerns of exposure error in both types of studies, some investigators have considered *capture area analyses* (O'Neill et al. 2005; Stölzel et al. 2007; Andersen et al. 2008a; Belleudi et al. 2010), where associations are reassessed in only the population that resides within a limited distance from the monitoring site. This restriction made a difference in the study by Andersen and colleagues (2008a): total NC was not significantly associated with daily wheezing in infants in the overall analyses (i.e., including children living within a 15-km radius of the monitor), but associations were significant when the analysis was limited to children living within a 5-kilometer radius of the monitor (Andersen et al. 2008a).

In panel studies, populations have also been chosen on the basis of their residence near the fixed-site monitor of interest — within 2 kilometers (Penttinen et al. 2001a,b; Song et al. 2011), 5 kilometers (Pekkanen et al. 2002; Lanki et al. 2008), or 10 kilometers (Anderson et al. 2010) — of the ambient monitoring site. It is difficult to assess the contribution of these geographical restrictions to detection of epidemiologic associations, however. Effects with NC measures were observed in only three of the six cited studies; these variable findings may be attributable to a range of factors other than exposure error (such as study population and outcome investigated).

Other efforts have been made to improve UFP field monitoring campaigns for panel studies. Several of the more recent panel studies have utilized more comprehensive exposure characterization, including school-based outdoor measurements (Song et al. 2011), home outdoor and indoor measurements (Delfino et al. 2008, 2009, 2010b,c; de Hartog et al. 2010), as well as personal exposure monitoring of NCs (Chan et al. 2004; Chuang et al. 2005). Many, but not all, of these studies reported associations between NC measures and the respective outcomes of interest.

Several of these articles allow for a comparison of epidemiologic results obtained from different exposure assessment approaches. In a European multicity study, de Hartog and colleagues (2010) found no consistent associations between total NC and pulmonary function, regardless of whether central site, home outdoor, or home indoor measurements were applied. Delfino and colleagues (2008), in their study of retirement home subjects, found stronger associations between total NC and markers such as IL-6 and CRP when using outdoor compared with indoor concentrations (note that indoor UFPs may have different size and chemical composition than outdoor UFPs). Associations using estimated indoor NC of outdoor origin, however, were more similar to those observed for outdoor concentrations. Figure 25 compares, for example, the results for IL-6 using outdoor and indoor NC (including indoor NC of ambient origin). The authors suggest that measurements recorded at outdoor home locations may be adequate to capture outdoor air pollution–cardiovascular health associations.

Epidemiologic Studies Using Measures of UFP Mass

Our review has until this point focused on studies that evaluated associations between UFPs characterized by number concentration measurements and health outcomes. As discussed in the Chapter 2 of this document, scientists have also characterized UFP concentrations using different measures of UFP mass. Measurements of reconstructed mass ($PM_{0.1}$) that more specifically target UFPs in the size range of interest for this document have been used to study source-apportionment of UFPs. However, these methods are only just beginning to be used in epidemiologic studies, and results have not yet been published. Some of the most detailed work done to date with PM mass has involved a larger particle size cut point, 250 nm, or $PM_{0.25}$ which is included in the class of particles commonly referred to as quasi-UFPs. Although these studies are not ideal for shedding light on UFPs (< 100 nm), we discuss them here in part because the investigators have made reasonable efforts to include data on particle number count and other air pollutants in their analyses. This work is also notable for providing some data on the composition of these smaller particle size fractions.

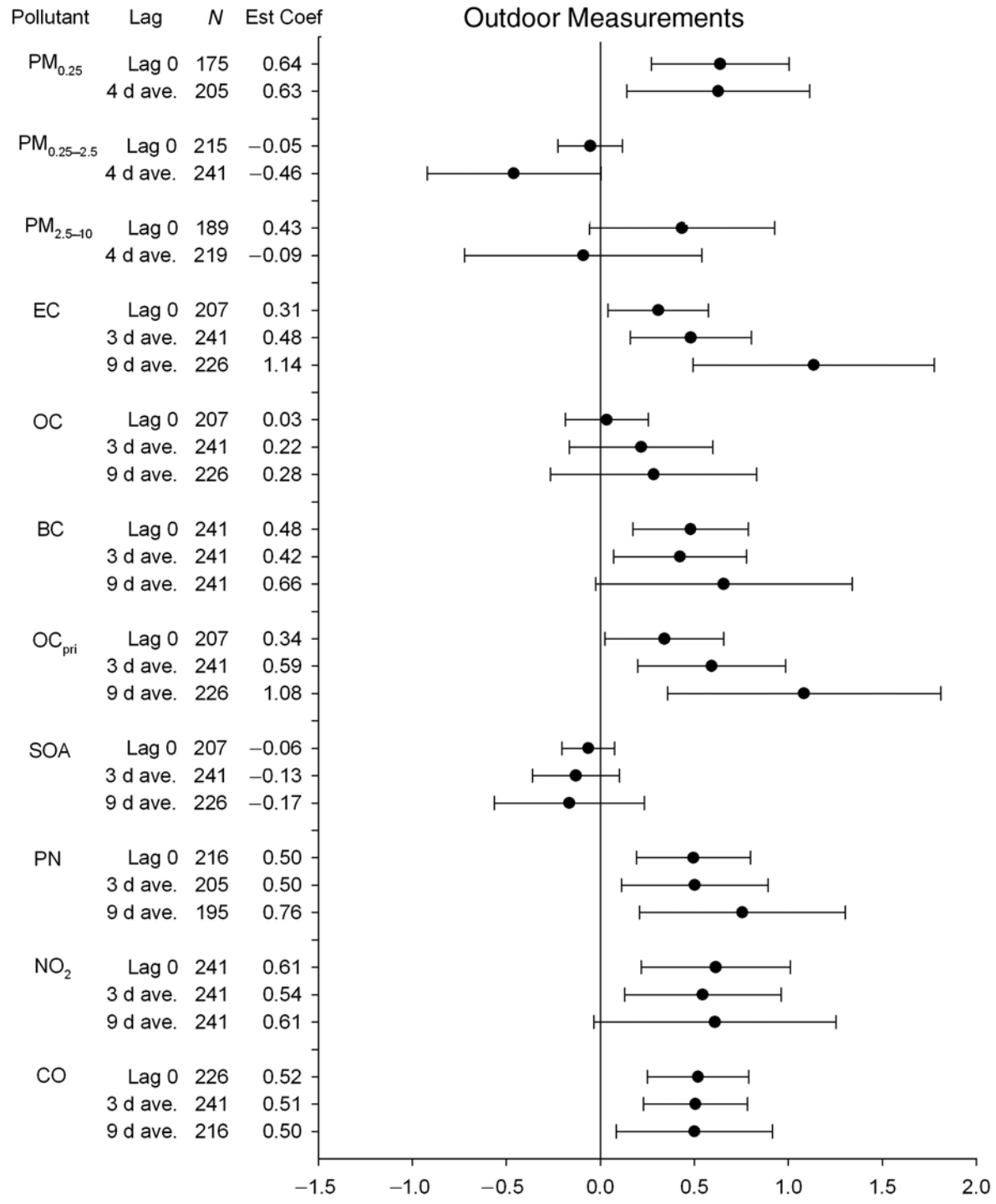

Figure 25. Comparison of the relationships of IL-6 (pg/mL), a biomarker of inflammation, to outdoor and indoor air pollutants. The figure plots the estimated change (adjusted coefficient and 95% CI) in IL-6 corresponding to an interquartile range change in the average air pollutant concentration for the previous day (lag 0), or for the previous several days preceding the blood draw). (Est Coef signifies estimated coefficient. For indoor measurements of EC, primary OC (OCpri), secondary organic aerosol (SOA), and PN, the symbol o_o signifies indoor concentrations of outdoor origin). (Source: Delfino et al. 2008, Figures 1 and 2, reproduced with permission from Environmental Health Perspectives.) (*Figure 25 continues on next page.*)

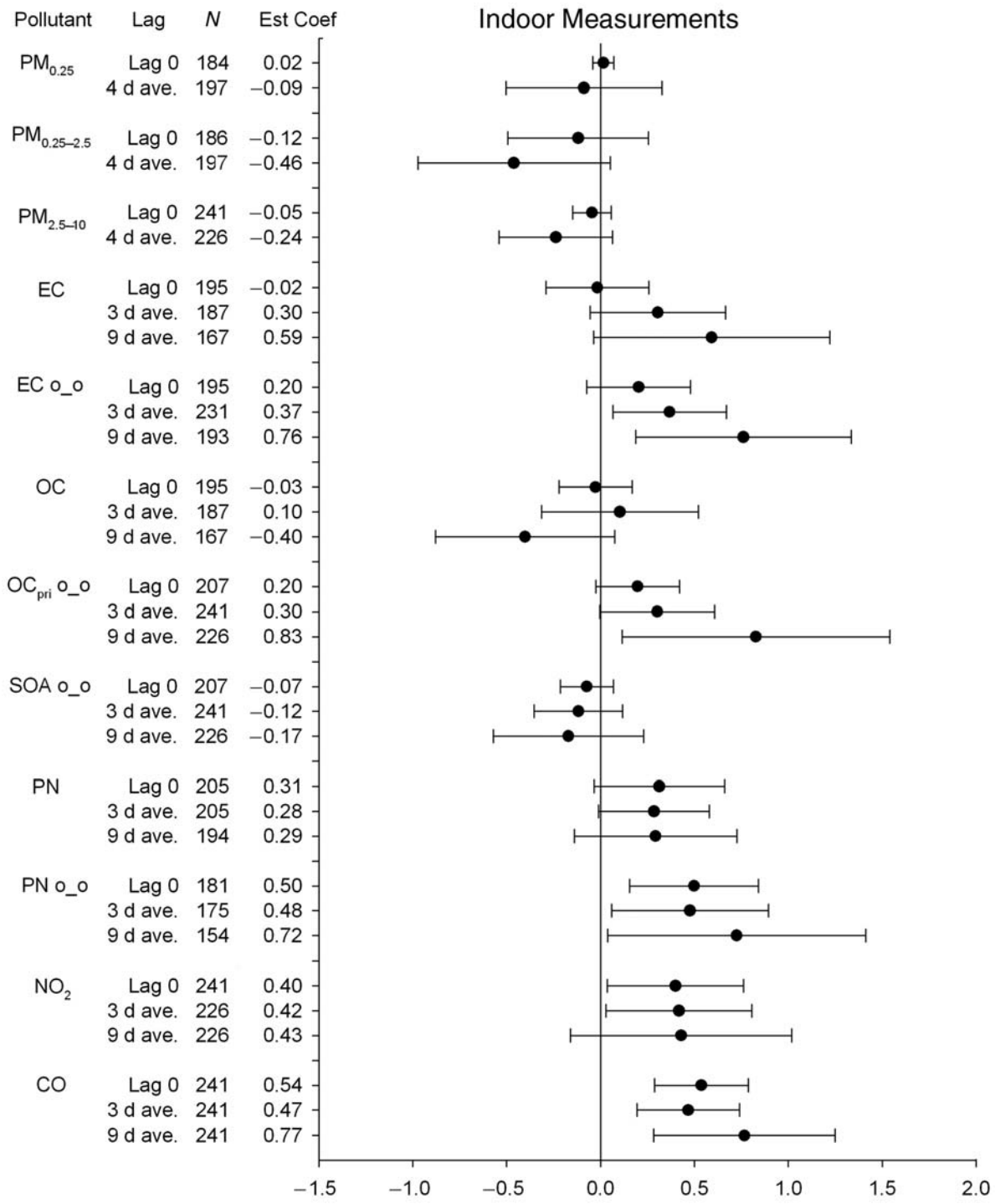

Figure 25 (*Continued*).

Two panel studies have assessed $PM_{0.25}$ mass concentration, either alone or alongside number concentration or other PM data. One is a study of patients with a previous myocardial infarction in Italy in which negative correlation was found between HRV and exposure to $PM_{0.25}$ in a group of patients not taking beta-blockers. More severe ventricular arrhythmias were observed at the highest concentrations of PM_{10} and $PM_{2.5}$. Indexes of inflammation in either breath condensate or blood did not correlate with PM exposures (Folino et al. 2009). The other is a series of panel studies of retirement home subjects with a history of coronary artery disease by Delfino and colleagues in Los Angeles, which has included perhaps the most detailed work to date on quasi-UFPs in an epidemiologic setting (Delfino et al. 2008; 2009; 2010a,b; 2011). Overall, the authors have observed associations between outdoor and indoor home $PM_{0.25}$ and ECG and blood marker outcomes. The group's recent analyses examined outdoor and indoor home measurements of $PM_{0.25}$ and $PM_{0.25}$ components (PAHs, hopanes, n-alkanes, organic acids, water-soluble OC, and transition metals) (Delfino et al. 2010b). The authors reported that strong associations with inflammatory markers (IL-6 and sTNF-RII) were observed with PAHs, and that associations of total $PM_{0.25}$ were confounded by $PM_{0.25}$ PAHs (see Figures 26 and 27). In a further analysis, the authors found both IL-6 and exhaled NO, a marker of pulmonary inflammation, were associated with $PM_{0.25}$ oxidative potential, which was assessed via reactive oxygen species generation in the in vitro cellular assays (Delfino et al. 2010a).

This study also included measurements of total NC, and therefore affords a comparison of results between the different UFP metrics. For example, in examination of the inflammatory markers the authors found associations with outdoor home measurements of both total NC and $PM_{0.25}$ (Delfino et al. 2009). In another analysis, however, the authors found ST-segment depression associated with outdoor home measurements of $PM_{0.25}$ (and other traffic-related pollutant measurements), but not with measurements of total NC (Delfino et al. 2011).

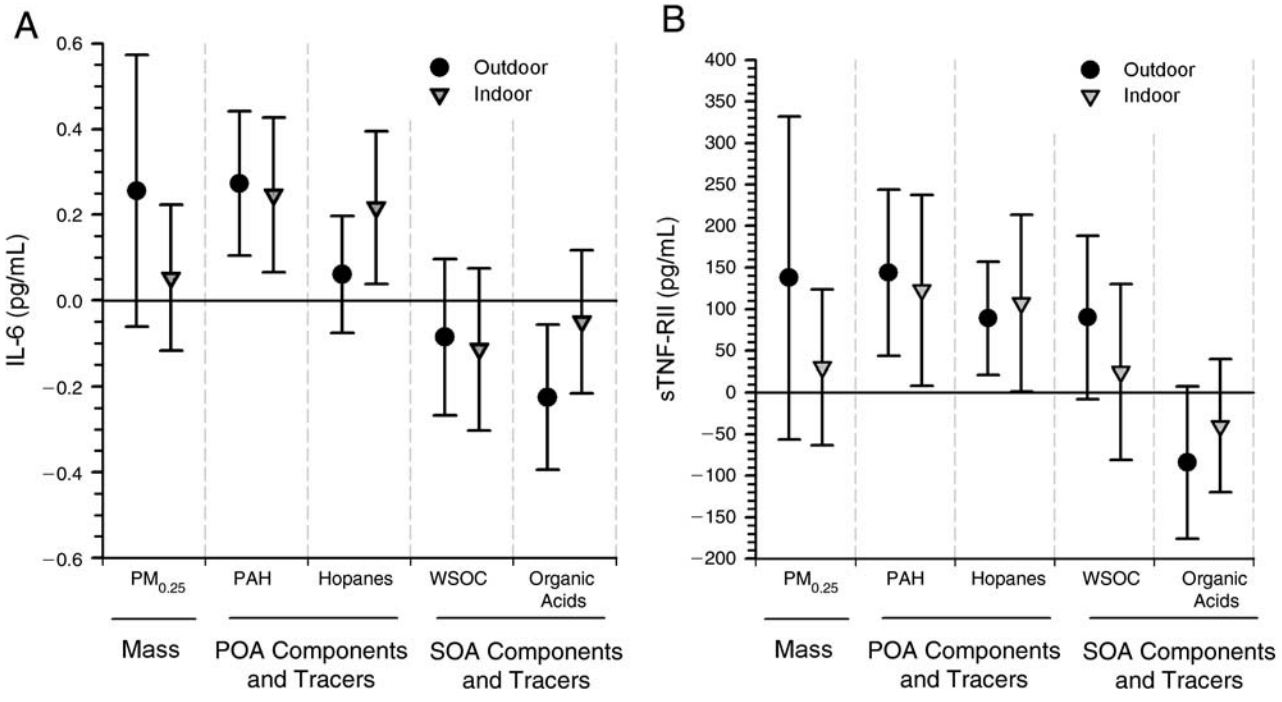

Figure 26. Associations of biomarkers of inflammation with 5-day average outdoor and indoor concentrations of $PM_{0.25}$ mass, and markers of primary organic aerosols (POAs) and secondary organic aerosols (SOAs) in subjects from a retirement community in Los Angeles, CA. The figure plots the expected change (adjusted coefficient and 95% CI) in **A:** IL-6 and **B:** sTNF-RII, corresponding to an IQR increase in the air pollutant concentration, adjusted for temperature. (Source: Delfino et al. 2010b, Figure 1, reproduced with permission from Environmental Health Perspectives.)

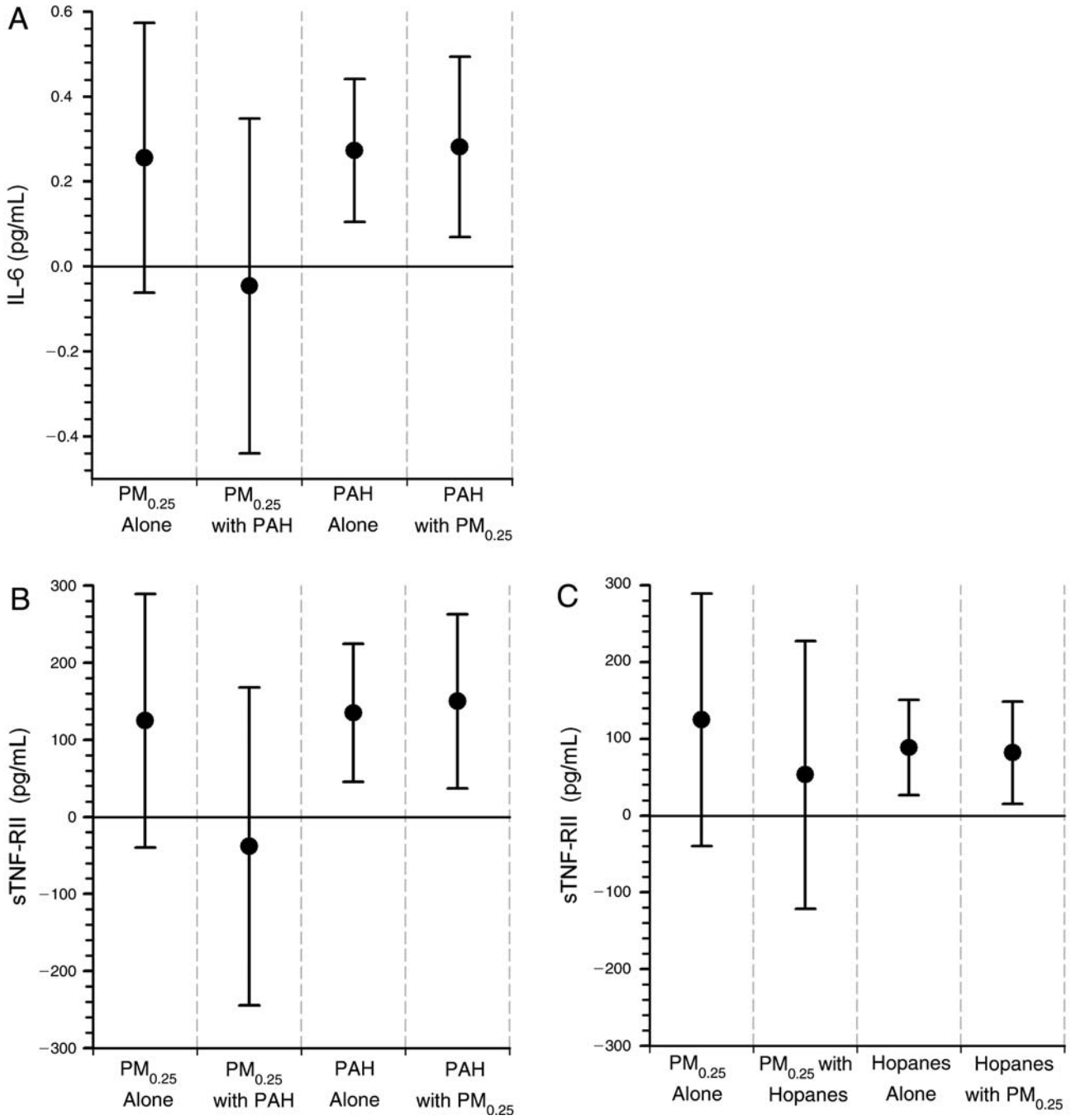

Figure 27. Associations of circulating biomarkers of inflammation with outdoor $PM_{0.25}$ mass coregressed with outdoor total PAHs and hopanes in $PM_{0.25}$ for subjects in a retirement community in Los Angeles, CA. A: IL-6, PAHs, and $PM_{0.25}$. **B:** sTNF-RII, PAHs, and $PM_{0.25}$. **C:** sTNF-RII, hopanes, and $PM_{0.25}$. Estimated change in the biomarker (adjusted coefficient and 95% CI) corresponds to an IQR increase in the air pollutant concentration, adjusted for temperature. (Source: Delfino et al 2010b, Figure 2, reproduced with permission from Environmental Health Perspectives.)

SUMMARY AND CONCLUSIONS FROM EPIDEMIOLOGY

For this issue of HEI Perspectives on UFPs, we reviewed both older summary reviews of the UFP epidemiologic literature and relevant primary research articles that have been published in the interval after the compilation of the 2009 EPA PM ISA (U.S. EPA 2009). A growing number of studies have attempted to assess the health effects of UFPs, either as their main focus or as one of several pollutants of interest. However, for reasons summarized below, we have found that the evidence to date continues to lack consistency and coherence with regard to our overarching question of whether ambient UFPs affect human health differently or independently from the effects of other particle or gaseous copollutants.

Inconsistency of Results by Endpoint

Previous review articles have noted that the current evidence base lacks a coherent set of studies designed to address specific hypotheses about the specific health endpoints (Araujo and Nel 2009; Lotti et al. 2009). While a growing number of studies have considered the effects of short-term UFP exposure, the consistency of effects for any one endpoint is still lacking. For both respiratory and cardiovascular outcomes that are assessed here, studies continue to show inconsistent results, with some studies reporting associations with UFP exposure (e.g., Von Klot et al. 2002; Andersen et al. 2008a; Song et al. 2011) while others do not (e.g., de Hartog et al. 2003, 2010; Timonen et al. 2004).

The inconsistencies in observed associations and lag structures may be due to a number of factors, including differences in study designs, populations examined, data availability and UFP metric utilized, differential measurement error across studies, different model strategies and confounder control (e.g., weather), and possibly differences in pollutant composition, concentration, or a combination of composition and concentration that might influence health risk. Studies based on small panels of subjects are limited in their generalizability, which likely also contributes to the lack of consistent effects across the small but growing numbers of epidemiologic studies of UFPs. Ultimately, as in any study, one explanation that must be considered is that a true underlying association does not exist. However, the meta-analysis necessary to more fully test this hypothesis would be difficult to implement, given the current study design differences across the available epidemiologic literature.

Exposure Assessment

While research on UFPs and human health effects appears to be improving over time with regard to the quality of exposure measurements (e.g., improved measurement equipment, exposure assessment with multiple monitors), most studies lacked significant conclusions regarding the potential effect of exposure measurement error on study results. UFP concentrations are known to be highly spatially variable within cities, yet many city-wide assessments of UFPs do not account for this high variability. Short-term studies of UFPs and health effects may avoid the spatial error component by analyzing temporal variations, but the assumption that temporal variations within a city are spatially uniform is not explicitly evaluated. As such, there is a concern that null findings for health effects of UFPs may be the result of exposure measurement error. In one study where investigators specifically attempted to improve the accuracy of the NC exposure assessment, however, associations between total NC and human health effects were still not observed, possibly due to other study design considerations (de Hartog et al. 2010).

Assessment of the Independence of UFP Effects

Where positive associations have been observed with UFPs, studies have not generally shown independent effects of UFPs, either in the absence of other exposures or in models adjusting for expected copollutant effects. While associations between UFPs and human health effects were observed for some outcomes, many studies did not account or adjust for the potential associations with gases or other particle metrics (even when effects of those other particle metrics or gases were observed), or potential copollutant exposures were not addressed or even included in the analysis. While proximity to traffic and other markers of traffic exposures imply exposure to UFPs, it is very challenging to separate the potential health effects of UFP exposure from the potential health effects of other exposures associated with traffic such as NO_2, CO, or noise.

This survey of the literature was intended to assess the state of the literature with the regard to the health effects that are potentially associated with UFP exposure. Despite a growing evidence base of observational studies of UFPs and improving measurement and exposure assessment approaches, there remain inconsistencies in reported results between studies of the same or similar health endpoints and suggestive, but not definitive, research findings. Research on the long-term exposure effects of UFPs is particularly absent from the literature. Given the emerging understanding of spatial and temporal exposure variation, the potential role of copollutants, evolving measurement methods and technology, and unclear physiologic mechanisms of action, the epidemiologic findings do not identify definitive, reproducible human health effects that are uniquely associated with UFP exposure.

CHAPTER 5. Summary and Conclusions

SUMMARY

Ever since the hazards of air pollution were first identified, scientists and policy makers have sought to identify those constituents of the air pollution mixture that might explain, in whole or in part, the adverse effects that have been observed. Over two decades ago, epidemiologic studies began to find that PM was associated with increased mortality and morbidity, but the underlying biological mechanisms for such relationships were the subject of much speculation. About the same time, researchers hypothesized that the components of PM, including UFPs, could be responsible for the adverse effects of PM and of the air pollution mixture in general. The motivation for research on these hypotheses was not just to understand the underlying mechanisms but to help ensure that efforts to control exposures to air pollution were targeted effectively on those components of most relevance to public health.

A substantial body of literature has now been published on the sources and generation 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 on UFPs has been to provide a broad assessment of what has been learned and what remains poorly understood. We structured our assessment of this literature and its ability to inform an answer to the overall objective as responses to three questions:

1. 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 varies 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 is changing rapidly with changes in fuels, engine, and exhaust aftertreatment technology. The collective effect of all these changes has not been thoroughly explored and is likely to 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 not routinely monitored, and most monitoring in studies relies primarily on measures of total NC and to a lesser extent on size-differentiated number concentrations. Particle number counts tell us little about other characteristics of UFPs, such as surface area, surface reactivity, or chemical composition, which may be of interest in understanding health effects. In addition, high covariation exists between UFPs and other combustion-related pollutants, such as CO and NO_x, near sources such as traffic. Furthermore, UFP NCs often differ substantially from one location to another in the same city. Consequently, reliance on measurements at central site monitors to represent broad population exposure, for example, across an entire metropolitan area — a central feature of epidemiologic of studies of long-term exposures to $PM_{2.5}$ and other pollutants — is more likely to lead to misclassification or errors in determining UFP exposure.

However, UFP NCs measured at multiple locations within cities do tend to vary temporally in similar patterns over the course of a day. Moderately good temporal correlations between UFP 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 of the effects of short-term variations of NCs on human health, with study designs that have been useful in studies of larger size fractions. However, the temporal variability in UFP NC is likely to be similar to that of other PM size fractions and gaseous pollutants, making it difficult to differentiate the effects of UFP NC in such study designs.

2. Do UFPs affect health? What is the evidence from experimental studies in animals and humans?

Experimental studies have provided evidence to indicate that, 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. Taken together, these findings provide a rationale for the hypothesis that the adverse health effects of exposure to UFPs differ from those of larger particles.

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. With the exception of brain effects, the findings are largely similar to those observed for exposures to fine particles.

There are limitations and inconsistencies in the findings on UFP health effects. There are no long-term animal exposure studies of UFP health effects. Relatively few studies have directly compared UFPs with other particle size fractions. The somewhat inconsistent findings in human controlled exposure (chamber) and real-world studies discussed in Chapter 3 likely result in part from differing outcome measures, as well as limitations in measurements, study designs, and statistical power. Furthermore, clinical studies of exposure to UFP proxies, such as laboratory-generated UFP or concentrated ambient UFP, may not accurately reflect the effects of exposure to actual ambient UFP under real-life conditions. On the other hand, the real-world studies of exposure to ambient UFPs face the challenges of disentangling the health effects of UFPs from other traffic-related pollutants.

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. The limitations of the experimental data, and the absence of long-term exposure studies in animals or humans, constrain our ability to draw definitive conclusions about the consequences of exposure to UFPs.

3. Do UFPs affect human health at environmental concentrations? What is the evidence from epidemiologic studies?

Epidemiologic 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 disease. 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 larger epidemiologic studies of air pollution health effects, in part because ambient monitoring of UFPs is not conducted in most locations; UFPs have been defined and measured in different ways; and the greater exposure measurement error for UFPs relative to $PM_{2.5}$ and other pollutants makes it difficult to design epidemiologic studies with sufficient 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 actually 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 published articles that cited any significant health associations with UFPs measured as NC, 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. It should be noted that multipollutant models are inherently difficult to interpret and may not be appropriate to implement with pollutants that are considered surrogates of the same source (e.g., traffic in this case).

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

CONCLUSIONS

Airborne PM has been the focus of extensive research and debate in the United States and around the world. At this point, 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 (U.S. EPA 2009; Brook et al. 2010; CASAC 2010). This evidence has provided the foundation for many regulatory decisions to limit both PM emissions, particularly 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?

In the years since investigators first became concerned about the potential adverse effects of exposure to the smallest of airborne particles, a considerable body of research has been conducted on the emissions, exposures, and health effects of UFPs. 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, toxicologic studies in animals, human exposure studies, and epidemiologic studies to date have not provided consistent findings of such effects with exposures to ambient levels of UFPs, particularly in human populations. The evidence also does not support a conclusion that exposures to UFPs alone can account in substantial ways for the adverse effects that have also been associated with other ambient pollutants such as $PM_{2.5}$.

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 can be ruled out. The limitations in the evidence base are attributable to underlying gaps in exposure data, to numerous challenges to comparison and synthesis of existing studies, and to the inherent complexity of the scientific task scientists have set out to accomplish. Similar kinds of issues face ongoing efforts to tease out the health significance of other components of the PM mixture (Brunekreef 2010; Bell 2012; Lippmann et al. in press; Vedal et al. in press). Fortunately, and irrespective of evidence for a specific role for UFPs, recent PM regulatory decisions affecting fuels, engine designs and exhaust aftertreatment in the United States, Europe, and Japan will result in the significant reduction in emissions of both fine and ultrafine particles.

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 this discussion, however, steps to address some of the limitations of the current evidence on UFPs should be considered.

Experimental Studies

Even in the absence of broad-scale epidemiologic evidence, insight into the potential toxicologic implications of differences in the deposition and retention of inhaled UFPs may still be possible with well-designed experimental studies of controlled exposures to UFPs and related copollutants. Examples include:

- **Further animal studies of the potential for, and health effects of, translocation and accumulation of UFPs in tissues beyond the lung, including the central nervous system.** This work should be extended to additional animal species and to models of human disease.
- **Animal inhalation studies of long-term exposures to UFPs.** Virtually all of the work to date has been with short-term exposures; the kind of evidence that has been so important for understanding the effects of long-term exposures to $PM_{2.5}$ and PM_{10} does not exist for UFPs.
- **Further human studies of UFP health effects and mechanisms.** Such studies should include both controlled laboratory exposures and real-world panel studies that target UFPs of various sources and chemical composition but also involve comparisons with various PM size fractions and copollutants.

Epidemiologic Studies

- **Studies of long-term exposure to ambient UFPs.** The kinds of data that have provided broad support for epidemiologic investigations of the public health implications of long-term exposure to $PM_{2.5}$ and PM_{10} — multiple years of monitoring data, using consistent methods, in major urban areas representing millions of people — have simply not existed for UFPs. Different approaches to characterizing exposure (discussed below in recommendations for characterization of ambient UFP exposures) need to be considered for long-term studies of UFP exposures to be possible.
- **Targeted study designs with sufficient contrasts in UFP exposure, but that improve the ability to characterize the independent effects of exposure to UFPs.** These might include scripted activities, measurements in environments with unique UFP exposure features, and studies of interventions that are specifically designed to control exposures to UFPs. Intervention study designs where investigators filter out exposures to UFPs or to particles of various size fractions, but not gases, may be informative here.
- **More consistent and comparable study designs.** One of the factors that has limited comparisons and interpretation of the epidemiologic studies conducted to date on the effects of short-term exposures to ambient UFPs is the variability in study designs, both in exposure methods and measurements (including copollutants) and in the health outcomes across individual studies and cities. The kinds of meta-analyses that have been used

successfully to strengthen inferences from short-term studies of $PM_{2.5}$ and PM_{10} in the United States, Europe, Asia, and Latin America are consequently challenging and, to our knowledge, have not been conducted. Even the more consistent multicity study designs desirable for meta-analyses, and that are beginning to be applied to the study of UFPs, may still yield equivocal results if they must rely primarily on central monitors or do not account appropriately for copollutants.

Better Characterization of Ambient UFP Exposures

Many of the underlying challenges posed by the existing evidence on ambient UFPs relate to differences in how they are measured across studies and how much data are available to assess exposures. In part, variation in approaches reflects the exploratory stage of efforts to identify size and other characteristics that might predict toxicity of UFPs. However, it is one of the factors limiting comparison and synthesis of the studies that have been done to date.

- **Find ways to exploit the high spatial variability of ambient UFPs in health studies.** As UFPs do show gradients in concentrations within urban areas that are related to traffic sources, spatial modeling approaches that have been used to assess health effects related to traffic pollution may be applicable to UFPs, although characterizing the role of UFPs within the traffic mixture will remain challenging.
- **Explore UFP metrics other than NC for these applications.** For example, UFP mass and chemical composition are more difficult to measure at an individual location, but population exposure to these metrics may be easier to predict using a combination of statistical models and reactive chemical-transport models. Linked with source-apportionment methods, such data could assist in identifying sources and allow monitoring of how changes to those sources would affect these temporal and spatial patterns in the future.
- **Consider the growing literature on new statistical and other analytic methods aimed at disentangling the sources, exposures, and health implications of PM components and other copollutants.** Although not discussed in this document, these methods are addressing many of the same basic issues as those faced in the study of UFPs.

Ultimately, it will be important to monitor the effect on ambient UFPs of actions taken that target the emissions of PM and other pollutants that may directly or indirectly affect ambient UFP concentrations. For motor vehicle sources, the primary focus of this document, the recent developments in motor vehicle technologies — exhaust aftertreatment systems and the development of new fuels — already suggest major changes in the absolute and relative importance of UFP and other pollutant emissions. The time course and impact of regulatory and technological changes on ambient concentrations and on human exposures will depend on a number of factors, including shifts in the size, age, and composition of the vehicle fleet in particular regions. However, without ongoing monitoring and evaluation in the years to come, questions about whether or not these changes have addressed the most important characteristics of the PM mixture will remain.

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Appendix Table A.1. Overview of HEI Research Program on UFPs

Research Report (RR) #; Author, Date	Report or Study Title	Summary	Related Journal Publications
Exposure Assessment			
RR 121; Cohen et al. 2004	Field Evaluation of Nanofilm Detectors for Measuring Acidic Particles in Indoor and Outdoor Air	Dr. Cohen and her colleagues at New York University School of Medicine tested the performance of a novel iron nanofilm substrate in the laboratory and the field to collect and measure sulfuric acid ultrafine particles under a variety of temperature and humidity conditions. They had hypothesized that acidic ultrafine particles could be particularly damaging to the lung. Particles were predominantly in the 35–100 nm range but could range up to 300 nm. The method was partially successful but required further development	Hazi et al. 2003
RR 173; Johnston et al., in press	Selective Detection and Characterization of Nanoparticles from Motor Vehicles	In this study, the authors field tested a Nanoaerosol Mass Spectrometer they had developed to provide real-time measurement and composition of nanoparticles particles sized 20–30 nm. They used the NAMS with other state-of-the art instruments to determine the composition of the nanoparticles and to identify the contribution of individual motor vehicles to ambient nanoparticles concentrations at a traffic intersection.	Klems et al. 2010; Klems et al. 2011; Zordan et al. 2010
In review; Stanier and Lee	"Development and application of a personal exposure screening model for size-resolved urban aerosols"	Dr. Stanier is constructing an exposure estimation model based on several existing models to predict ultrafine particle formation from secondary photochemical processes and from vehicle exhaust in large urban areas.	
In review; Zhu et al.	"Assessing children's exposure to ultrafine particles from vehicular emissions"	Dr. Zhu is measuring ultrafine particle levels in classrooms and school buses under a variety of conditions, including different diesel engine exhaust after treatment devices, traffic density, and ventilation.	Zhang and Zhu 2010

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Appendix Table A.1 (*Continued*). Overview of HEI Research Program on UFPs

Research Report (RR) #; Author, Date	Report or Study Title	Summary	Related Journal Publications
Animal and in vitro Exposures			
RR 96; Oberdörster et al. 2000	Acute Pulmonary Effects of Ultrafine Particles in Rats and Mice	Dr. Oberdörster and colleagues at the University of Rochester School of Medicine and Dentistry hypothesized that inhaled ultrafine particles induce an inflammatory response in the airways of mice and rats and that animals with preexisting airway inflammatory conditions may be particularly vulnerable. The investigators focused on inhaled carbon and platinum particles because these elements are constituents of particles found in urban atmospheres. The investigators tested a small number of young and old mice and rats that were healthy or had preexisting airway inflammatory conditions. Pulmonary inflammation was evaluated by measurement of cellular and biochemical parameters in bronchoalveolar lavage fluid, focusing on increases in the percentage of neutrophils and production of reactive oxygen species, which appeared to be the most sensitive indicators of a response. The HEI Health Review Committee concluded that the study provided little evidence that inhaled ultrafine particles cause inflammation, a result it thought could be attributed to small numbers of animals and experiments, and uncertainties about the animal model, the relative toxicity of the particles studied. More research was advised.	Elder et al. 2000a; Elder et al. 2000b; Elder et al. 2000c; Johnston et al. 1998; Johnston et al. 1999; Johnston et al. 2000a; Johnston et al. 2000b
RR 129; Hahn et al. 2005	Particle Size and Composition Related to Adverse Health Effects in Aged, Sensitive Rats	Dr. Hahn and colleagues systematically examined lung inflammation in young adult and old rats after inhalation of fine particles (< 2.5 µm) and ultrafine particles (< 0.1 µm, ~median diameter 35 nm) of different composition: relatively inert carbon and vanadium pentoxide (V_2O_5), which contains the transition metal vanadium, known to cause toxic effects upon inhalation in humans in occupational settings. In addition, they examined the effect of a short-term increase (spike) in particle exposure concentration on inflammatory response. They found greater retention of ultrafine V_2O_5 particles and more evidence of inflammation in aged rats compared with fine particles. Spikes in ultrafine and fine particle levels increased the inflammatory response at some, but not all concentrations.	
RR 135; Pinkerton et al. 2008	Mechanisms of Particulate Matter Toxicity in Neonatal and Young Adult Rat Lungs	Dr. Pinkerton and colleagues designed a study to determine whether the biologic response to inhaled ultrafine particles depends on particle composition. Neonatal and young adult rats were exposed to laboratory-generated ultrafine metal particles (mean 70–80 nm), either alone or in combination with soot (60% EC, 40% OC), and their lungs examined for oxidative stress, inflammation, and injury. The results suggested that some markers of oxidative stress and inflammation were higher for exposures to combinations of iron and soot than to either particle type alone.	Pinkerton et al. 2004; Yang et al. 2001; Zhou et al. 2003a; Zhou et al. 2003b

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Appendix Table A.1 (*Continued*). Overview of HEI Research Program on UFPs

Research Report (RR) #; Author, Date	Report or Study Title	Summary	Related Journal Publications
Animal and in vitro Exposures (*Continued*)			
RR 136; Kennedy et al. 2009	Uptake and Inflammatory Effects of Nanoparticles in a Human Vascular Endothelial Cell Line	This report describes a one-year study to evaluate which physicochemical characteristics (size, shape, agglomeration, calculated surface area) of metal nanoparticles may contribute to their toxicity. Nanoparticles of oxides of iron, zinc, yttrium, and cerium were generated in the laboratory and characterized in detail, followed by preliminary studies of particle uptake and inflammatory effects in human endothelial cells exposed to these nanoparticles. The study found that different metal oxide particles induced different levels of biologic responses, but could not distinguish whether these effects were also attributable to differences in their physical properties. In particular, biological responses were inversely correlated with calculated surface area, an unexpected and unexplained result.	Gojova et al. 2007; Gojova et al. 2009
RR 164; Nurkiewicz et al. 2011	Pulmonary Particulate Matter and Systemic Microvascular Dysfunction	Dr. Nurkiewicz and colleagues evaluated whether exposure to fine or nano-sized titanium dioxide (TiO_2) particles may affect cardiovascular endpoints, in particular endothelium-dependent vascular dilation. Rats were exposed via inhalation to 0.5 to 20 mg/m^3 TiO_2 for up to 12 hours and evaluated for vascular dilation and for markers of oxidative stress, coagulation, and inflammation. The study demonstrated that the degree of systemic microvascular dysfunction associated with PM exposure is related to the size and lung burden of the particles, that the nanoparticles were more potent at an equivalent lung burden, and that was mediated by decreased NO production in endothelial cells. Whether this effect of nanoparticles was related to particle surface area could not be determined. Evidence of lung inflammation was weak and a role of systemic inflammatory mediators was not clearly established.	Nurkiewicz et al. 2008; Nurkiewicz et al. 2009; Prisby et al. 2008
In review; Q. Zhang et al.	"Activation of endothelial cells and gene expression in lungs following exposure to ultrafine particles"	Dr. Zhang is investigating effects of exposure to ultrafine particles on endothelial cells in the lungs of apolipoprotein E (ApoE) knockout mice and their healthy counterparts.	Mo et al. 2009; Wan et al. 2008
RR 177; Lippmann et al., in press	National Particle Component Toxicity Study: Health Effects of PM Components in Mice, and Cells In vitro	Using 3 different size fractions of concentrated ambient particles collected in 5 US locations representing diverse ambient air pollution conditions, the authors conducted subchronic inhalation studies in mice in order to identify the $PM_{2.5}$ constituents most responsible for acute and cumulative effects; They also investigated the role of chemical composition in $PM_{10–2.5}$, $PM_{2.5–0.2}$, and $PM_{<0.2}$ on in vitro and in vivo acute toxicity in the same five locations.	Lippmann and Chen 2009

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Appendix Table A.1 (*Continued*). Overview of HEI Research Program on UFPs

Research Report (RR) #; Author, Date	Report or Study Title	Summary	Related Journal Publications
Human Controlled Exposures			
RR 118; Gong et al. 2003	Controlled Exposures of Health and Asthmatic Volunteers to Concentrated Ambient Particles in Metropolitan Los Angeles	Funded at the same time as the Frampton study, the Gong study focused on exposures to 12 healthy and 12 mildly asthmatic individuals but to 'worst case' concentrations of fine particles concentrated from ambient air in Los Angeles (mean 174 μg/m^3). The two studies shared similar designs, exposure protocols, and health endpoints in order to provide a better basis for comparison of the results for fine and ultrafine particles. The study found that their CAPs exposures induced few cardiovascular, pulmonary function, or airway or systemic inflammatory effects in either healthy or asthmatic individuals. For the few significant changes observed, effects were small and demonstrated no consistent patterns. Sensitivity of the study for the most endpoints appeared sufficient.	Chang et al. 2000; Gong 2000; Gong et al. 2002; Kim et al. 2000; Sioutas et al. 2000
RR 126; Frampton et al. 2004	Effects of Exposure to Ultrafine Carbon Particles in Healthy Subjects and Subjects with Asthma	Dr. Frampton and his colleagues evaluated the effects of exposing 12 healthy and 16 mildly asthmatic men and women to laboratory-generated ultrafine carbon particles (elemental carbon, count median diameter is 25 nm). They hypothesized that ultrafine particle exposure would activate leukocytes and endothelial cells and lead to an inflammatory response in the airway and in the blood; and that it also might affect respiration and cardiac electrophysiologic function. The investigators evaluated markers of airway inflammation in sputum and in blood, and pulmonary and cardiac function before, during, and after a 2-hour exposure to concentrations of 10–25 μg/m^3 particles while at rest or with intermittent exercise. The number and mass of inhaled particles that deposited in the lungs of the participants were calculated. The study found few ultrafine particle-associated airway, systemic, or cardiac electrophysiologic changes in either healthy or asthmatic individuals. The HEI Review Committee concluded that the clinical significance of the small changes that were observed was not clear and that additional study was needed to provide a stronger test of the hypothesis that ultrafine particles are more toxic than larger ones.	Chalupa et al. 2002; Chalupa et al. 2004; Daigle et al. 2003; Frampton 2001; Frampton et al. 2000; Pietropaoli et al. 2004a; Pietropaoli et al. 2004b; Utell, Frampton 2000; Utell et al. 2002
RR 138; J. Zhang et al. 2009	Health Effects of Real-World Exposure to Diesel Exhaust in Persons with Asthma	Dr. Zhang and colleagues evaluated how inhaling air with a high concentration of diesel exhaust from vehicular traffic while walking on a busy street in Central London might affect people who had either mild or moderate asthma. They evaluated pulmonary function parameters, bronchial reactivity, and markers of airway inflammation and oxidative stress in participants who walked for two hours along Oxford Street, where vehicles are predominantly diesel-powered, and in Hyde Park, where there is urban background air pollution and no traffic.	McCreanor et al. 2007

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Appendix Table A.1 (*Continued*). Overview of HEI Research Program on UFPs

Research Report (RR) #; Author, Date	Report or Study Title	Summary	Related Journal Publications
Epidemiology			
RR 98; Wichmann et al. 2000	Daily Mortality and Fine and Ultrafine Particles in Erfurt, Germany, Part 1: Role of Particle Number and Particle Mass	Dr. H-Erich Wichmann and colleagues at the National Research Center for Environment and Health in Germany prospectively studied the association of daily mortality data with size-fractionated mass and number concentrations of ultrafine and fine particles in Erfurt, Germany, using Poisson regression techniques. Concentrations were measured near a road and a time-series approach was used to look at short-term changes in particle concentration and concurrent deaths due to cardiovascular and respiratory causes over a period of 3.5 years. The study found similar associations between mortality and ultrafine and fine particulate size fractions. The HEI Review Committee however concluded the study did not provide support for a relative or temporal difference in the effects of ultrafine and fine particles.	
RR 124 Part I; Peters et al. 2005	Air pollution, personal activities, and onset of myocardial infarction in a case–crossover study. In: Particulate Air Pollution and Nonfatal Cardiac Events	Dr. Peters and her colleagues evaluated the association between nonfatal myocardial infarction (MI) and exposure to particulate matter just prior to the event. 691 patients in hospitals in Augsburg, Germany, who survived an MI were asked to provide hourly details about their activities 4 days before MI onset. The investigators used a case–crossover analysis to determine whether exposure to pollutants was associated with onset of MI. They measured levels of ultrafine particles, $PM_{2.5}$ and PM_{10} in ambient air and obtained information about levels of gaseous pollutants (NO_2, CO, SO_2, and ozone), and local weather conditions. No associations were found between elevated concentrations of particulate air pollution and MI hours later, or between ultrafine particles and MI onset within 5 days.	Peters et al. 2004; Stölzel et al. 2007

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Appendix Table A.1 (*Continued*). Overview of HEI Research Program on UFPs

Research Report (RR) #; Author, Date	Report or Study Title	Summary	Related Journal Publications
Epidemiology (*Continued*)			
RR 124 Part II; Dockery et al. 2005b	Association of air pollution with confirmed arrhythmias recorded by implanted defibrillators. In: Particulate Air Pollution and Nonfatal Cardiac Events	Dr. Dockery and colleagues assessed the correlation between short-term increases in ambient concentrations of particulate matter and the risk of possibly life-threatening arrhythmias in patients with implanted cardioverter defibrillators (ICDs). An ICD is programmed to respond when the heart rate exceeds a preset number of beats per minute; it records and stores the heartbeat pattern during an arrhythmic episode and (if necessary) delivers an electrical stimulus to return the heart rate to a normal rhythm. The investigators studied 195 patients from Boston, MA, who had either single or dual-chamber ICD's and used logistic regression models to determine whether exposure to pollutants ($PM_{2.5}$, ultrafine particles, black carbon, sulfate, NO_2, CO, SO_2, and ozone) was associated with arrhythmias. In addition, they evaluated patients' clinical information in some analyses to determine whether specific characteristics (e.g., diagnosis at ICD implantation, medication use, occurrence of multiple arrhythmias) would modify a pollutant's effects. The study found that nonfatal arrhythmic events were weakly, but not significantly associated with ambient concentrations of $PM_{2.5}$ or black carbon up to 3 days before the event. Similar findings were reported for ultrafines (total particle number) and sulfate. Of all pollutants evaluated, SO_2 showed the strongest and most robust associations although associations were also observed with NO_2 and CO.	Dockery et al. 2005a; Rich et al. 2005
Special Report 17 HEI 2010	Traffic-Related Air Pollution: A Critical Review of the Literature on Emissions, Exposure, and Health Effects	This report is the most comprehensive and systematic review to date of the scientific literature on emissions, exposure, and health effects from traffic-related air pollution. It includes conclusions about the populations exposed around major roads, the associations between exposure to air pollution from traffic and human health, and important remaining data gaps.	
Communication 16 HEI 2011	The Future of Vehicle Fuels and Technologies: Anticipating Health Benefits and Challenges	This report reviews new vehicle fuels and technologies that are likely to be commercially available within the next 10 years in the United States and other industrialized countries at a level that could result in significant population exposure. It highlights expected changes in emissions and other effects from the use of each technology and fuel, along with any life-cycle and regulatory issues. This Communication was prepared by the Special Committee on Emerging Technologies (SCET) whose 18 members include government, academic, industrial, and other experts from diverse fields, including automotive engineering and emissions, emissions control technologies, new fuels, electric vehicles, and environmental modeling. The report identifies many high-priority areas for research. In response, the HEI Research Committee has developed an Action Plan that describes the steps the Committee is taking, or plans to take, to address the high-priority issues identified by SCET.	

Appendix Table B.1. Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Mortality								
Prague, Czech Republic	Braniš et al. 2010	Time series	2006	**$NC_{0.05–0.2}$**	SMPS	Central	NC_{32}, NC_{115}, NC_{365}, $PM_{2.5}$	No
London, England	Atkinson et al. 2010	Time series	2000–2005	Total NC	CPC	Central	$PM_{2.5}$	$PM_{2.5}$
Helsinki, Finland	Halonen et al. 2009	Time series	1998–2004	**$NC_{0.03–0.1}$**	DMPS	Central	$PM_{2.5}$, nucleation mode, Aitken mode, accumulation mode, $PM_{2.5–10}$	No
	Kettunen et al. 2007	Time series	1998–2004	**$NC_{<0.1}$**	DMPS	Central	NO_2, O_3, CO, $PM_{2.5}$, PM_{10}, $PM_{2.5–10}$	$PM_{2.5}$, CO
Erfurt, Germany	Breitner et al. 2009	Time series	1991–2002	**$NC_{0.01–0.1}$**	AS	Central	CO, NO_2, $PM_{2.5}$, PM_{10}	CO, NO_2, $PM_{2.5}$, PM_{10}
	Peters et al. 2009	Time series	1991–2002	$NC_{0.003–0.064}$, $NC_{0.01–0.03}$, **$NC_{0.01–0.1}$**	AS	Central	CO, NO_2, SO_2, O_3, $NC_{0.01–0.1}$, $NC_{0.01–2.5}$, $PM_{2.5}$, PM_{10}	CO, NO_2, O_3
	Stölzel et al. 2003	Time series	1995–1998	**$NC_{0.01–0.1}$**	MAS	Central	Not reported	SO_2, NO_2, CO, $PM_{2.5}$
	Stölzel et al. 2007	Time series	1995–2001	**$NC_{0.01–0.1}$**	MAS	Central	CO, NO_2, NO, PM_{10}, NC, and MC size fractions	NO, NO_2, CO
	Wichmann et al. 2000	Time series	1995–1998	**$NC_{0.01–0.1}$**	MAS	Central	CO, NO_2, SO_2, $PM_{2.5}$	CO, NO_2, SO_2, $PM_{2.5}$

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a APC = aerosol particle counter; AS = aerosol spectrometer; BC = black carbon; BS = black smoke; CPC = condensation particle counter; DMA = differential mobility analyzer; DMPS = differential mobility particle sizer; EAS = electric aerosol spectrometer; MAS = mobile aerosol spectrometer; MC = mass concentration; NC = particle number concentration; PAHs = polycyclic aromatic hydrocarbons; PMF = positive matrix factorization; SMPS = scanning mobility particle sizer; SOC – secondary organic carbon; TDMPS = twin differential mobility particle sizer; WSOC = water soluble organic carbon.

b Study abbreviations: AIRGENE = Athens, Augsburg, Barcelona, Helsinki, Rome, Stockholm; NAS = Normative Aging Study; PEACE = Pollution Effects in Asthmatic Children in Europe; RUPIOH = Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health; ULTRA = Exposure and Risk Assessment for Fine and Ultrafine Particles in Air.

c Diameter size ranges are in micrometers (μm). Several articles considered multiple size fractions. The bolded metric is the one closest to the definition used in this document (i.e., < 0.100 μm in diameter or UFP NC).

d These are two-pollutant models unless otherwise indicated.

Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Mortality (*Continued*)								
Rome, Italy	Forastiere et al. 2005	Case–crossover	1998–2000	Total NC	CPC	Central	CO, NO_2, SO_2, O_3, PM_{10}	PM_{10}
Beijing, China	Breitner et al. 2011	Time series	2004–2005	$NC_{0.003–0.03}$, **$NC_{0.03–0.1}$** (also related MC and SC size fractions)	TDMPS	Central	Between all particle size fractions	Selected NC size fractions
Morbidity								
Prague, Czech Republic	Branis et al. 2010	Time series	2006	$NC_{0.05–0.2}$	SMPS	Central	$PM_{2.5}$, $NC_{32, 115, 365}$	No
Copenhagen, Denmark	Andersen et al. 2008b	Time series	2001–2004	$NC_{0.06–0.7}$ **$NC_{<0.1}$**	DMPS	Central	NO_2, O_3, CO, other NC size fractions, PM_{10}, $PM_{2.5}$	CO, NO_2, O_3, PM_{10}, $PM_{2.5}$ Multi-pollutant models: NC size fractions, PM_{10}
	Andersen et al. 2010	Case–crossover	2003–2006	**$NC_{<0.1}$**	DMPS	Central	NO_x, CO, PM_{10}	NO_x, CO, PM_{10}
	Iskandar et al. 2012	Case–crossover	2001– 2008	**$NC_{0.01–0.7}$**	DMPS	Central	NO_x, NO_2, PM_{10}, $PM_{2.5}$	NO_x, NO_2, PM_{10}, $PM_{2.5}$
London, England	Atkinson et al. 2010	Time series	2000–2005	Total NC	CPC	Central	$PM_{2.5}$, PM_{10}, $PM_{2.5–10}$, NO_3^-, SO_4^{2-}, BS	Particles $PM_{2.5}$, PM_{10}, BS

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a APC = aerosol particle counter; AS = aerosol spectrometer; BC = black carbon; BS = black smoke; CPC = condensation particle counter; DMA = differential mobility analyzer; DMPS = differential mobility particle sizer; EAS = electric aerosol spectrometer; MAS = mobile aerosol spectrometer; MC = mass concentration; NC = particle number concentration; PAHs = polycyclic aromatic hydrocarbons; PMF = positive matrix factorization; SMPS = scanning mobility particle sizer; SOC – secondary organic carbon; TDMPS = twin differential mobility particle sizer; WSOC = water soluble organic carbon.

b Study abbreviations: AIRGENE = Athens, Augsburg, Barcelona, Helsinki, Rome, Stockholm; NAS = Normative Aging Study; PEACE = Pollution Effects in Asthmatic Children in Europe; RUPIOH = Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health; ULTRA = Exposure and Risk Assessment for Fine and Ultrafine Particles in Air.

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Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Morbidity (*Continued*)								
Helsinki, Finland	Halonen et al. 2008	Time series	1998–2004	$NC_{<0.03}$ $NC_{0.03–0.1}$	DMPS	Central	NO_2, CO, $PM_{2.5}$, O_3	NO_2, CO, $PM_{2.5}$
	Halonen et al. 2009	Time series	1998–2004	$NC_{0.03–0.1}$	DMPS	Central	$PM_{2.5}$, nucleation mode, Aitken mode, accumulation mode, $PM_{2.5–10}$	No
Leipzig, Germany	Franck et al. 2011	Panel (cross-sectional)	1997–2002	$NC_{>0.3}$ $NC_{>0.5}$	APC	Personal	PM_1, $PM_{2.5}$	No
Rome, Italy	Belleudi et al. 2010	Case–crossover	2001–2005	Total NC	CPC	Central	PM_{10}, $PM_{2.5}$	PM_{10}, $PM_{2.5}$
5-Cities (HEAPPS)	Lanki et al. 2006	Time series	1992–2000	Total NC	CPC & retrospective estimation	Central	CO, NO_2, O_3, PM_{10}	O_3, PM_{10}
	Von Klot et al. 2005	Time series	1992–2001	Total NC	CPC & retrospective estimation	Central	CO, NO_2, O_3, PM_{10}	O_3, PM_{10}
Atlanta, GA	Metzger et al. 2004	Time series	1993–2000	**$NC_{0.01–0.1}$**	SMPS	Central	O_3, NO_2, CO, SO_2, PM_{10}, $PM_{2.5}$	No
	Peel et al. 2005	Time series	1993–2000	**$NC_{0.01–0.1}$**	SMPS	Central	CO, NO_2, $PM_{2.5}$, OC, $PM_{2.5}$, EC	No
	Sinclair and Tolsma 2004	Time series	1998–2000	**$PM_{0.01–0.1}$** area	SMPS	Central	No	No

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a APC = aerosol particle counter; AS = aerosol spectrometer; BC = black carbon; BS = black smoke; CPC = condensation particle counter; DMA = differential mobility analyzer; DMPS = differential mobility particle sizer; EAS = electric aerosol spectrometer; MAS = mobile aerosol spectrometer; MC = mass concentration; NC = particle number concentration; PAHs = polycyclic aromatic hydrocarbons; PMF = positive matrix factorization; SMPS = scanning mobility particle sizer; SOC – secondary organic carbon; TDMPS = twin differential mobility particle sizer; WSOC = water soluble organic carbon.

b Study abbreviations: AIRGENE = Athens, Augsburg, Barcelona, Helsinki, Rome, Stockholm; NAS = Normative Aging Study; PEACE = Pollution Effects in Asthmatic Children in Europe; RUPIOH = Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health; ULTRA = Exposure and Risk Assessment for Fine and Ultrafine Particles in Air.

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d These are two-pollutant models unless otherwise indicated.

Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Morbidity (*Continued*)								
Beijing, China	Leitte et al. 2011	Time series	2004–2006	**$NC_{< 0.1}$**	TDMPS	Central	NO_2, SO_2, NC size fractions	NO_2, PM_{10}
Respiratory Symptoms								
Copenhagen, Denmark	Andersen et al. 2008a	Panel (repeated measure)	1998–2004	**$NC_{0.1–0.7}$**	DMPS	Central	NO_2, NO_x, CO, O_3, $PM_{2.5}$, PM_{10}	NO_2, NO_x, CO, PM_{10}
Kuopio, Finland	Tiitanen et al. 1999	Panel (repeated measure)	1995	**$NC_{0.01–0.1}$**	EAS	Central	CO, SO_2, NO_2, O_3, PM_{10}, $PM_{2.5}$, $PN_{0.1–1.0}$, BC	$PM_{2.5}$, PM_{10}
Helsinki, Finland	Penttinen et al. 2001b	Panel (repeated measure)	1996–1997	**$NC_{0.01–0.1}$**, $NC_{0.01–10}$	EAS + CPC	Central	CO, NO, NO_2, PM_{10}, $PM_{2.5–10}$, $PM_{2.5}$, PM_1, $NC_{0.01–0.1}$, $NC_{0.1–1}$, $NC_{0.01–10}$	CO, NO, NO_2 (with $NC_{0.01–10}$ only)
Erfurt, Germany	Peters et al. 1997	Panel (repeated measure)	1991–1992	$NC_{0.01–2.5}$, **$NC_{0.01–0.1}$**, $NC_{0.1–0.5}$, $NC_{0.5–2.5}$, (and related MC fractions)	Electrical mobility analyzer + CPC	Central	NC size fractions, MC fractions, PM_{10}	PM_{10}, $MC_{0.1–0.5}$
	Von Klot et al. 2002	Panel (repeated measure)	1996–1997	**$NC_{0.01–0.1}$**, $NC_{0.1–0.5}$, $NC_{0.5–2.5}$, (and related MC fractions)	DMA + CPC	Central	NO_2, CO, SO_2, $NC_{0.1–0.5}$, $NC_{0.5–2.5}$, $MC_{0.1–0.5}$, $MC_{0.5–2.5}$, $PM_{2.5–10}$, PM_{10}	NO_2, SO_2, CO

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a APC = aerosol particle counter; AS = aerosol spectrometer; BC = black carbon; BS = black smoke; CPC = condensation particle counter; DMA = differential mobility analyzer; DMPS = differential mobility particle sizer; EAS = electric aerosol spectrometer; MAS = mobile aerosol spectrometer; MC = mass concentration; NC = particle number concentration; PAHs = polycyclic aromatic hydrocarbons; PMF = positive matrix factorization; SMPS = scanning mobility particle sizer; SOC – secondary organic carbon; TDMPS = twin differential mobility particle sizer; WSOC = water soluble organic carbon.

b Study abbreviations: AIRGENE = Athens, Augsburg, Barcelona, Helsinki, Rome, Stockholm; NAS = Normative Aging Study; PEACE = Pollution Effects in Asthmatic Children in Europe; RUPIOH = Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health; ULTRA = Exposure and Risk Assessment for Fine and Ultrafine Particles in Air.

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Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Respiratory Symptoms (*Continued*)								
Aberdeen, Scotland	Osunsanya et al. 2001	Panel (repeated measure)	NA	**$NC_{<0.1}$**	SMPS	Central	PM_{10}	No
Amsterdam, Erfurt, Helsinki (ULTRA study)	de Hartog et al. 2003	Panel (repeated measure)	1998–1999	**$NC_{0.01–0.1}$** Total NC	AS + CPC	Central	Total NC, $PM_{2.5}$	Yes, not reported
Incheon, South Korea	Song et al. 2011	Panel (repeated measure)	2009	**$NC_{0.01–0.1}$**, $NC_{0.11–1}$, $NC_{0.01–1}$	SMPS + CPC	Central	NO_2, SO_2, CO, PM_1, $PM_{2.5}$, PM_{10}	PM_{10}, $PM_{2.5}$, PM_1
Pulmonary Function								
Kuopio, Finland (PEACE study)	Pekkanen et al. 1997	Panel (repeated measure)	1994	$NC_{0.010–0.032}$, **$NC_{0.032–0.10}$**, $NC_{0.10–0.32}$, $NC_{0.32–1.0}$, $NC_{1.0–3.2}$, $NC_{3.2–10}$	EAS	Central	NO, NO_2, CO, SO_2, black smoke, NC size fractions	NO_2, NO, SO_2
	Tiitanen et al. 1999	Panel (repeated measure)	1995	**$NC_{0.01–0.1}$**	EAS	Central	CO, SO_2, NO_2, O_3, PM_{10}, $PM_{2.5}$, $NC_{0.1–1.0}$, BC	$PM_{2.5}$, PM_{10}, NO_2, SO_2, O_3

Table continues next page

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Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Pulmonary Function (*Continued*)								
Helsinki, Finland	Penttinen et al. 2001a	Panel (repeated measure)	1996–1997	**$NC_{0.01–0.1}$**, $NC_{0.1–1}$, $NC_{0.01–10}$	EAS	Central	PM_{10}, $PM_{2.5}$, PM_1, NC size fractions	No
	Penttinen et al. 2001b	Panel (repeated measure)	1996–1997	**$NC_{0.01–0.1}$**, $NC_{0.01–10}$	EAS	Central	CO, NO, NO_2, PM_{10}, $PM_{2.5–10}$, $PM_{2.5}$, PM_1, $NC_{0.01–0.1}$, $NC_{0.1–1}$, $NC_{0.01–10}$	For $NC_{0.01–10}$ only: CO, NO, NO_2
Erfurt, Germany	Peters et al. 1997	Panel (repeated measure)	1991–1992	$NC_{0.01–2.5}$, **$NC_{0.01–0.1}$**, $NC_{0.1–0.5}$, $NC_{0.5–2.5}$, (and related MC fractions)	Electrical mobility analyzer + CPC	Central	NC size fractions, MC fractions, PM_{10}	PM_{10}, $MC_{0.1–0.5}$
Aberdeen, Scotland	Osunsanya et al. 2001	Panel (repeated measure)	NA	**$NC_{<0.1}$**	SMPS	Central	PM_{10}	No
Amsterdam Athens Birmingham Helsinki (RUPIOH study)	de Hartog et al. 2010	Panel (repeated measure)	2002–2004	Total NC	CPC	Central, outdoors, indoors	PM_{10}, $PM_{2.5}$, $PM_{2.5–10}$	No

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Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Pulmonary Function (*Continued*)								
Arnhem, the Netherlands	Zuurbier et al. 2011b	Panel (repeated measure)	2007–2008	Total NC	CPC	Personal	$PM_{2.5}$, PM_{10}, soot	No
Ottawa, Canada	Weichenthal et al. 2011	Panel (repeated measure)	2010	**$NC_{\leq 0.1}$**	CPC	Personal	CO, SO_2, NO_2, O_3, $PM_{2.5}$, BC	O_3, BC
HRV								
Erfurt, Germany	Schneider et al. 2010	Panel (repeated measure)	2000–2001	**$NC_{0.01–0.1}$**	MAS	Central	$PM_{2.5}$, EC, OC	No
Aberdeen, Scotland	Barclay et al. 2009	Panel (repeated measure)	2003–2005	**$NC_{0.01–0.1}$**	SMPS	Central, personal (estimated)	NO_2, NO, $PM_{2.5}$, PM_{10}	No
Amsterdam, Erfurt, Helsinki (ULTRA Study)	Timonen et al. 2006	Panel (repeated measure)	1998–1999	**$NC_{0.01–0.1}$**, $NC_{0.01–1}$	AS + CPC	Central	NO_2, CO, $NC_{0.01–1}$, $PM_{2.5}$, $PM_{2.5–10}$	NO_2, CO, O_3, $PM_{2.5}$
Boston, MA	Park et al. 2005	Panel (cross-sectional)	2000–2003	Total NC	CPC	Central	No	No

Table continues next page

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Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
HRV (*Continued*)								
New Jersey	Laumbach et al. 2010	Panel (pilot study)	NA	$NC_{0.01–1.0}$	CPC	Personal	CO, NO_2, $PM_{2.5}$	No
Taipei, Taiwan	Chan et al. 2004	Panel (cross-sectional)	NA	$NC_{0.02–1}$	P-Trak Ultrafine particle counter	Personal	No	No
Rochester, NY	Rich et al. 2012	Panel (repeated measure)	2006–2009	**$NC_{0.01–0.1}$** $NC_{0.1–0.5}$	Wide range particle spectrometer	Central	$PM_{2.5}$, $NC_{0.1–0.5}$	$PM_{2.5}$, $NC_{0.1–0.5}$
Ottawa, Canada	Weichenthal et al. 2011	Panel (repeated measure)	2010	$NC_{0.01–1}$	CPC	Personal	CO, SO_2, NO_2, O_3, $PM_{2.5}$, BC	O_3, BC
Arrhythmia and Related Endpoints								
London, England	Anderson et al. 2010	Case–crossover	1995–2003	Total NC	CPC	Central	CO, SO_2, O_3, NO_X, NO, NO_2, SO_4, $PM_{2.5}$, PM_{10}, BS	No
Augsburg, Germany	Hampel et al. 2010	Panel (repeated measure)	2003–2004	Total NC	CPC	Central	CO, NO_2, $PM_{2.5}$, $PM_{2.5–10}$, PM_{10}	No

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Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Arrhythmia and Related Endpoints (*Continued*)								
Erfurt, Germany	Berger et al. 2006	Panel (repeated measure)	2000–2001	**$NC_{0.01–0.1}$**, $NC_{0.1–1}$	MAS	Central	CO, NO, NO_2, SO_2, $NC_{0.1–1}$, $PM_{2.5}$	No
	Henneberger et al. 2005	Panel (repeated measure)	2000–2001	**$NC_{0.01–0.1}$**, $NC_{0.01–1}$	MAS	Central	NO, NO_2, CO, $PM_{2.5}$, $NC_{0.01–1}$, EC, OC	No
	Yue et al. 2007	Panel (repeated measure)	2000–2001	**$NC_{0.01–0.1}$**, NC source factors (PMF)	MAS	Central	No	No
Aberdeen, Scotland	Barclay et al. 2009	Panel (repeated measure)	2003–2005	**$NC_{0.01–0.1}$**	SMPS	Central, personal (estimated)	NO_2, NO, $PM_{2.5}$, PM_{10}	No
Eastern MA	Dockery et al. 2005a,b	Case–crossover	1995–2002	Total NC	CPC	Central	No	No
Ischemia								
Helsinki, Finland (ULTRA study)	Lanki et al. 2008	Panel (repeated measure)	1999	**$NC_{<0.1}$**	EAS	Central	Outdoor $PM_{2.5}$, personal $PM_{2.5}$	No
	Pekkanen et al. 2002	Panel (repeated measure)	1998–1999	**$NC_{0.01–0.1}$**, $NC_{0.1–1}$	EAS	Central	CO, NO_2, $PM_{2.5–10}$, $PM_{2.5}$, PM_1, $NC_{0.1–1}$	$PM_{2.5}$, PM_1, $NC_{0.1–1}$

Table continues next page

a APC = aerosol particle counter; AS = aerosol spectrometer; BC = black carbon; BS = black smoke; CPC = condensation particle counter; DMA = differential mobility analyzer; DMPS = differential mobility particle sizer; EAS = electric aerosol spectrometer; MAS = mobile aerosol spectrometer; MC = mass concentration; NC = particle number concentration; PAHs = polycyclic aromatic hydrocarbons; PMF = positive matrix factorization; SMPS = scanning mobility particle sizer; SOC – secondary organic carbon; TDMPS = twin differential mobility particle sizer; WSOC = water soluble organic carbon.

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Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Ischemia (*Continued*)								
Los Angeles, CA	Delfino et al. 2011	Panel (repeated measure)	2005–2007	Total NC **$PM_{0.25}$**	CPC, Sioutas Personal Cascade Impactor Sampler	Central & indoor	O_3, CO, NO_x, $PM_{2.5–10}$, $PM_{2.5}$, $PM_{0.25–2.5}$, $PM_{0.25}$, OC, BC	No
Vascular Reactivity								
Boston, MA	O'Neill et al. 2005	Panel (cross-sectional)	1998–2002	Total NC	CPC	Central	SO_4^{2-}, BC, $PM_{2.5}$	No
Ottawa, Canada	Dales et al. 2007	Panel (repeated measure)	NA	$NC_{0.02–1}$	P-Trak Ultrafine Particle Counter	Personal	$PM_{2.5}$	No
Blood Pressure								
Ottawa, Canada	Dales et al. 2007	Panel (repeated measure)	NA	$NC_{0.02–1}$	P-Trak Ultrafine Particle Counter	Personal	$PM_{2.5}$	No
Taipei, Taiwan	Chuang et al. 2005	Panel (repeated measure)	NA	$NC_{0.02–1}$	P-Trak Ultrafine Particle Counter	Personal ($NC_{0.02–1}$), Central	CO, NO_2, PM_{10}	CO, PM_{10}

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Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Blood Pressure (*Continued*)								
Los Angeles, CA	Delfino et al. 2010c	Panel (repeated measure)	2005–2007	Total NC	CPC	Central (outdoor home)	CO, NO_x, O_3, BC, OC	No
Rochester, NY	Rich et al. 2012	Panel (repeated measure)	2006–2009	**$NC_{0.01–0.1}$**, $NC_{0.1–0.5}$	Wide range particle spectrometer	Central	$PM_{2.5}$, $NC_{0.1–0.5}$	$PM_{2.5}$, $NC_{0.1–0.5}$
Amsterdam, Erfurt, Helsinki (ULTRA Study)	Ibald-Mulli et al. 2004	Panel (repeated measure)	1998–1999	**$NC_{0.01–0.1}$**, $NC_{0.1–1}$	EAS	Central	SO_2, CO, NO_2, $NC_{0.1–1}$, $PM_{2.5}$	No
Soluble Markers of Inflammation, Coagulation, and Oxidative Stress[e]								
Augsburg, Germany (AIRGENE study)	Brüske et al. 2011*	Panel (repeated measure)	2003–2004	**$NC_{<0.1}$**	CPC	Central	O_3, SO_2, NO, CO. $PM_{2.5}$, PM_{10}	No
	Kraus et al. 2011*^	Panel (repeated measure)	2003–2004	Total NC	CPC	Central	$PM_{2.5}$, hopanes, PAHs	No

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e Markers examined: * systemic inflammation; ^ coagulation; # oxidative stress.

Appendix Table B.1 (*Continued*). Primary Research Articles Presenting Results of Total and UFP NC Epidemiologic Studies by Outcome and Geographic Location[a]

Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Soluble Markers of Inflammation, Coagulation, and Oxidative Stress (*Continued*)[e]								
Erfurt, Germany	Brüske et al. 2010*	Panel (repeated measure)	2001–2002	**$NC_{0.01–0.1}$**, $NC_{0.1–1}$	MAS	Central	CO, NO, NO_2, SO_2, OC, EC, PM_{10}, $NC_{0.1–1}$	CO, NO_2
	Hildebrandt et al. 2009*^	Panel (repeated measure)	2001–2002	**$NC_{0.01–0.1}$**, $NC_{0.1–1}$	DMPS, CPC + SMPS	Central	$NC_{0.1–1}$	No
	Rückerl et al. 2006*^	Panel (repeated measure)	2000–2001	**$NC_{0.01–0.1}$**, $NC_{0.1–1}$	MAS	Central	CO, NO_2, $PM_{2.5}$, PM_{10}	No
	Rückerl et al. 2007b*	Panel (repeated measure)	2000–2001	**$NC_{0.01–0.1}$**, $NC_{0.1–1}$	MAS	Central	NO, $PM_{2.5}$, PM_{10}	No
	Yue et al. 2007*	Panel (repeated measure)	2000–2001	**$NC_{0.01–0.1}$**	MAS, with factor analysis by PMF	Central	No	No

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Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	UFP Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Soluble Markers of Inflammation, Coagulation, and Oxidative Stress (*Continued*)[e]								
Ruhr area, Germany	Hertel et al. 2010*	Panel (cross-sectional)	2000–2003	Total NC	NA	Residence modeled from central site using European Air Pollution and Dispersion Model (EURAD)	No	No
Aberdeen, Scotland	Barclay et al. 2009*^	Panel (repeated measure)	2003–2005	**$NC_{0.01–0.1}$**	SMPS	Central, personal (estimated)	NO_2, NO, $PM_{2.5}$, PM_{10}	No
Arnhem, the Netherlands	Zuurbier et al. 2011a*^	Panel (repeated measure)	2007–2008	Total NC	CPC (TSI 3007)	Personal	$PM_{2.5}$, PM_{10}, soot	No
6-Cities (AIRGENE study)	Ljungman et al. 2009*	Panel (repeated measures)	2003–2004	Total NC	CPC	Central	CO, NO_2	No
	Rückerl et al. 2007a*^	Panel (repeated measure)	2003–2004	Total NC	CPC	Central	Not reported	No

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Outcome / Location[b]	Reference	Study Design	Study Period	Selected UFP Metric[c]	Sampling Equipment	Exposure Assignment	Copollutant Correlations	Copollutants in Two-Pollutant Models?[d]
Soluble Markers of Inflammation, Coagulation, and Oxidative Stress (*Continued*)[e]								
Boston, MA (NAS)	Ren et al. 2011#	Panel (cross sectional)	2006–2008	Total NC	Not reported	Central	CO, O_3, SO_4^{2-}, NO_2, BC, EC, $PM_{2.5}$	No
	Zeka et al. 2006*^	Panel (cross sectional)	2000–2004	$NC_{0.007–3}$	CPC	Central	SO_4^{2-}, BC, $PM_{2.5}$	No
Rochester, NY	Rich et al. 2012	Panel (repeated measure)	2006–2009	**$NC_{0.01–0.1}$**, $NC_{0.1–0.5}$	Wide range particle spectrometer	Central	$PM_{2.5}$, $NC_{0.1–0.5}$	$PM_{2.5}$, $NC_{0.1–0.5}$
Los Angeles, CA	Delfino et al. 2008*^	Panel (repeated measure)	2005–2006	Total NC	CPC	Central & indoor	No	No
	Delfino et al. 2009*#	Panel (repeated measure)	2005–2007	Total NC	CPC	Central	O_3, CO, NO_2, NO_x, OC, BC, SOC, $PM_{0.25}$, $PM_{0.25–2.5}$, $PM_{2.5–10}$	No
	Delfino et al. 2010b*	Panel (repeated measure)	2005–2007	**$PM_{0.25}$**	Sioutas Personal Cascade Impactors	Central & indoor	Organic components of $PM_{0.25}$ (PAHs, hopanes, WSOC, n-Alkanes, organic acids)	PAHs, hopanes

a APC = aerosol particle counter; AS = aerosol spectrometer; BC = black carbon; BS = black smoke; CPC = condensation particle counter; DMA = differential mobility analyzer; DMPS = differential mobility particle sizer; EAS = electric aerosol spectrometer; MAS = mobile aerosol spectrometer; MC = mass concentration; NC = particle number concentration; PAHs = polycyclic aromatic hydrocarbons; PMF = positive matrix factorization; SMPS = scanning mobility particle sizer; SOC – secondary organic carbon; TDMPS = twin differential mobility particle sizer; WSOC = water soluble organic carbon.

b Study abbreviations: AIRGENE = Athens, Augsburg, Barcelona, Helsinki, Rome, Stockholm; NAS = Normative Aging Study; PEACE = Pollution Effects in Asthmatic Children in Europe; RUPIOH = Relationship between Ultrafine and fine Particulate matter in Indoor and Outdoor air and respiratory Health; ULTRA = Exposure and Risk Assessment for Fine and Ultrafine Particles in Air.

c Diameter size ranges are in micrometers (μm). Several articles considered multiple size fractions. The bolded metric is the one closest to the definition used in this document (i.e., < 0.100 μm in diameter or UFP NC).

d These are two-pollutant models unless otherwise indicated.

e Markers examined: * systemic inflammation; ^ coagulation; # oxidative stress.

ABBREVIATIONS AND OTHER TERMS

ACES	Advanced Collaborative Emissions Study
AMS	aerosol mass spectrometer
APC	aerosol particle counter
AS	aerosol spectrometer
BC	black carbon
BP	blood pressure
BS	black smoke
CAP	concentrated ambient particles
CASAC	Clean Air Scientific Advisory Committee
CNG	compressed natural gas
CO	carbon monoxide
COPD	chronic obstructive pulmonary disease
CPC	condensation particle counter
CRP	C-reactive protein
CVD	cardiovascular disease
DE	diesel exhaust
DISI	direct injection spark ignition
DMA	differential mobility analyzers
DMPS	differential mobility particle sizer
DPF	diesel particle filters
EAS	electric aerosol spectrometer
EC	elemental carbon
ECG	electrocardiogram
EEPS	engine exhaust particle sizer
ELPI	electrical low pressure impactor
FEV_1	forced expiratory volume in 1 sec
FMPS	fast mobility particle sizer
FVC	forced vital capacity
HR	heart rate
HRV	heart-rate variability
ICD	implanted cardioverter defibrillator
ICRP	International Commission on Radiological Protection
Ig	immunoglobulin
IL	interleukin
MAS	mobile aerosol spectrometer
MC	mass concentration
MOUDI	micro-orifice uniform deposit impactor
NAMS	nanoaerosol mass spectrometer
NC	number concentration
NF-κB	DNA transcription factor NF-κB
NO_x	nitrogen oxides
NO	nitric oxide
NO_2	nitrogen dioxide
NPACT	National Particle Component Toxicity
O_3	ozone
OC	organic carbon
OVA	ovalbumin
PAHs	polycyclic aromatic hydrocarbons
PEF	peak expiratory flow
PM	particulate matter
$PM_{2.5}$	PM ≤ 2.5 μm in aerodynamic diameter
PM_{10}	PM ≤ 10 μm in aerodynamic diameter
PM ISA	Integrated Science Assessment for Particulate Matter
PMF	positive matrix factorization
SCR	selective catalytic reduction
SMPS	scanning mobility particle sizer
TDMPS	twin differential mobility particle sizer
TNFα	tumor necrosis factor alpha
UF1	UFPs > 3 nm
UF2	UFPs > 15 nm
UFP	ultrafine particle
UFP NC	UFP number concentration
ULTRA	Exposure and risk assessment for fine & ultrafine particles in ambient air, a European Union-funded study
U.S. EPA	U.S. Environmental Protection Agency
VACES	versatile aerosol concentrator enrichment system
WSOC	water soluble organic carbon

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