PART I

ISSUE FRAMING
CHAPTER 1

OVERVIEW

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INTRODUCTION

Air pollution can lead to a wide range of detrimental health effects, including premature mortality. The reduction in life expectancy is very small for the population as a whole, but can be appreciable for those having preexisting disease or genetically based risk factors. An estimated 3 million deaths each year are attributed to air pollution, representing 5% of the 55 million deaths occurring annually in the world (World Health Organization [WHO] statistics). The London smog of December 1952 caused 4000–12,000 (Ministry of Health, 1954; Bell et al., 2004) excess deaths, and, despite the dramatic decreases in levels of air pollution that have been achieved since then, the association between air pollution and cardiopulmonary morbidity and mortality persists and has been widely established (Dockery et al., 1993; Anderson et al., 1996; Pope et al., 2002). Air pollutants implicated as potentially harmful include particulate matter (PM), nitrogen dioxide (NO₂), ozone (O₃), sulfur dioxide (SO₂), and volatile organic compounds (VOCs). Worldwide, authorities (WHO, United Nations, European Union [EU]) have declared that the most significant global air pollution health risk is posed by PM. To health risk reductions, ambient air quality standards have been set in the form of limit values. For PM, the standards are based on the airborne mass concentration of particles of the size that enter the thoracic airways and those that reach the deepest parts of the lungs—typically defined as having aerodynamic diameters centered on 10μm (PM₁₀) or 2.5μm (PM₂.₅). Despite the inherent limitations of a mass-based standard, that is, (1) the assumption of equivalent toxicity of all sampled particles and (2) the sampling and analytic artifacts that limit the accuracy and precision of measured PM concentrations, there is a substantial body of epidemiological evidence for statistically significant associations between airborne PM concentrations and excess mortality and morbidity. In some of the world’s 20 largest cities, peak concentrations of PM₁₀ may exceed 1000μg/m³, with average levels in the range of 200–600μg/m³, and only three of these cities have levels of PM pollution within current WHO guidelines (United Nations Environment Program Statistics) or standards (see Chapter 24).
Recent work comparing North American cities with different average air pollution in the period 1999–2000 indicated that living in a region with a 10 μg/m³ elevation in PM$_{2.5}$ was associated with a 6%, 8%, and 13% increase in the risk of all-cause, cardiopulmonary, and lung cancer mortalities, respectively (Pope et al., 2002). Similar figures have been presented for Europe.

Epidemiological literature demonstrates that there are statistically significant associations between airborne concentrations of fine PM (PM$_{2.5}$) and the rates of mortality and morbidity in human populations. PM$_{2.5}$ concentrations have almost always been expressed in terms of mass, although some studies suggest that number concentration, dominated by ultrafine PM (UFP), may correlate better with some effects than does mass concentration (Peters et al., 1997; Wichmann et al., 2000). Also, in studies that reported on associations between health effects and more than one index of mass concentration, the strength of the association generally improves as one goes from a formerly used index, that is, total suspended PM (TSP) to thoracic PM, also known as PM less than 10 μm in aerodynamic diameter (PM$_{10}$), to PM$_{2.5}$. In recent years, there is an emerging literature base that shows associations between some components of PM$_{2.5}$ and health-related effects that are stronger than those for overall PM$_{2.5}$.

**SIZES AND SOURCES**

PM is a complex mixture that is emitted from various sources and is composed of droplets and solid particles that differ in size and composition (see Chapters 4 and 5). Different size distribution modes in the ambient air in which we live and breathe can be identified for airborne particles produced by a broad variety of processes and are often classified into coarse thoracic (2.5–10 μm), fine (<2.5 μm), and ultrafine (<0.1 μm) size ranges. The larger particles are mostly derived from soil and crustal elements, whereas the smallest particles are primarily produced from the combustion of fossil fuels in motor vehicles or in power generation. Fine particles remain suspended for days to weeks, travel further (i.e., hundreds to thousands of kilometers) than coarse fraction particles, and are relatively more uniformly dispersed across urban and regional scales than coarse fraction particles or UFPs.

Particles can be of anthropogenic origin, or can originate from natural sources such as sea salt, soil dust, and spores. Particle sizes in the submicrometer size range can also be divided into three modes based in their origins and behavior in air: nucleation mode, Aitken mode, and accumulation mode (see Chapter 4). The main difference between these modes is their characteristic size range: nucleation mode <10 nm, Aitken mode 10–100 nm, and accumulation mode 200–1000 nm.

Ultrafine fine particles usually originate from combustion processes, such as engine exhaust or wild fires, and consist of carbonaceous compounds and transition metals such as Vi, Ni, and Zn. Fine mode PM is mainly composed of varying proportions of several major components: inorganic ions (H$^+$, NH$_4^+$, NO$_3^-$, and SO$_4^{2-}$); elemental carbon (EC); organic carbon (OC) compounds; trace elements; and water. As a result of the fundamentally different chemical compositions and sources of fine
and coarse fraction particles, the chemical composition of the sum of these two fractions, \( \text{PM}_{10} \), is more heterogeneous than either mode alone. Coarse fraction constituents are primarily crustal in origin, consisting of insoluble oxides of Si, Ca, Al, Fe, and K. Biological material such as bacteria, pollen, and spores may also be found in the coarse mode. Coarse mode particle may also carry smaller-sized particles on their surface. Coarse mode PM is generally produced by mechanical processes like wind erosion and abrasion and is not further discussed in detail in this introductory chapter.

Primary fine particles are formed from the condensation of high temperature vapors during combustion. Secondary fine particles are usually formed from gases in three ways: (1) nucleation (i.e., gas molecules coming together to form a new particle), (2) condensation of gases onto existing particles, and (3) by reaction of absorbed gases in liquid droplets. Particles formed by nucleation also coagulate to form relatively larger aggregate particles or droplets with diameters between 0.1 and 1.0 \( \mu \text{m} \), and such particles normally do not grow into the coarse mode. Particles form as a result of chemical reaction of gases (acidic sulfur, nitrogen oxide compounds) in the atmosphere that lead to products that either have a low enough vapor pressure to form a particle or react further to form a low vapor pressure substance.

All of these physicochemical aspects of PM affect exposure, internal dose, and the types of responses in humans (Chapters 6–8).

### EXTENT OF POPULATION EXPOSURES TO FINE PM AND UFP IN AMBIENT AIR

The concentrations of constituents of PM in the ambient air are important determinants of human responses to exposure to PM of outdoor origin, but other factors also greatly influence exposure (Chapter 5). For exposures occurring indoors, where most people spend most of their time, these include (1) limited penetrability of UFP and coarse mode PM to indoor spaces, (2) removal to indoor surfaces, and (3) chemical transformations. Each of these factors tends to reduce exposures to PM of outdoor origin for people spending time indoors.

The penetrability of PM into the indoor environment varies with the air exchange between outdoors and indoors, which, in turn, varies with building size, type of construction, heating and cooling systems, and wind velocity. There will also be variations by season, with minimal air exchange in midwinter and, for air-conditioned homes, in midsummer as well. Particle size affects penetrability, especially when infiltration pathways are reduced to save energy. Under such conditions coarse particle penetration can be greatly reduced.

Once PM penetrates indoors, particle size and chemical composition become major determinants of its fate. Coarse particles deposit relatively rapidly by sedimentation under the generally quiescent conditions indoors. UFP diffuse to and deposit on the walls and other indoor surfaces. Acidic particles will be neutralized by ammonia released into the indoor air by people, pets, and household products. Thus, the indoor/outdoor concentration ratio can be close to unity for a
component such as $\text{SO}_4^{2-}$, which is (1) present in the ambient air almost entirely in the accumulation mode (0.1–1 $\mu$m), (2) is chemically nonreactive, and (3) has no indoor sources in most circumstances.

For many constituents of outdoor PM, there are significant indoor sources, and the ratio of personal exposure to outdoor concentration for many substances can be much greater than unity. Major indoor PM sources include smoking and cooking.

**NATURE OF THE EVIDENCE FOR HUMAN HEALTH EFFECTS OF AMBIENT AIR PM**

For ambient air PM, significant associations between elevated concentrations and excess human mortality, morbidity, and lost time, as well as reduced lung function, have been described. However, except under the most extreme exposure conditions, such as in Donora, PA, in 1948 (Schrenk et al., 1949), where nearly half of the population reported morbidity (which may have been due to the relatively high exposure to Zn fume), only a small percentage of the population was observed to suffer these adverse effects. Furthermore, the affected populations are generally limited to those who are very young or elderly, and within these groups, those with preexisting disease or special sensitivity. In this context, the lack of confirming data and mechanistic understanding of the basis for the adverse effects from controlled human and animal inhalation studies should come as no great surprise. Short-term human exposure studies can seldom be ethically conducted on especially vulnerable subjects, and chronic long-term exposure studies on humans that may produce cumulative damages that are unethical. Controlled inhalation studies on laboratory animals having enhanced sensitivity, and using concentrated ambient air PM often referred to as CAPs, have recently been reported, and some of them have produced mortality and changes in atherosclerosis progression and brain cell distributions, as well as fatty liver changes, development of metabolic syndrome (MS), and functional changes in the lungs and heart that are consistent with the epidemiological findings (Lippmann and Chen, 2009).

While evidence is accumulating that some specific PM components (Ni, V, Zn, EC) are especially influential in producing adverse health effects, it is also possible that the effects associated with ambient air PM are initiated by nonspecific responses or reactions to deposited particles by lung epithelial cells that can be triggered by most, if not all, deposited particles. In that case, the appropriate index of challenge may be associated with the number of depositing particles, or the number having a surface area or volume greater than some threshold level. In the following sections, we describe recent literature that demonstrates significant associations between cardiovascular effects and PM components and/or source-related PM mixtures. However, at this point, more research is needed before such associations can be established as being causal. The earlier literature is largely limited to associations of mortality and morbidity with traditional measure of PM concentrations.
Acute Exposures to Ambient Air PM

Much of the literature from the early 1990s was summarized by Pope et al. (1995a). They converted historically measured values for coefficient of haze (CoH) and TSPs to estimated levels of PM$_{10}$, and remarked that very similar coefficients of response for the PM$_{10}$ daily mortality associations were determined in all locations. In Thurston’s (1995) analysis of acute mortality studies in nine communities with measured PM$_{10}$ concentrations, including 4 of the 10 studies cited by Pope et al. (1995a), the coefficients of response tended to be higher when the PM$_{10}$ was expressed as a multiple-day average concentration, and lower when other air pollutants were included in multiple regression analyses. In any case, the results in each city (except for the very small city of Kingston, TN) indicated a statistically significant association. An extensive review is also provided in Chapter 2, and some examples are presented below.

The number of time-series studies of the associations between daily mortality and morbidity, and ambient air concentrations of PM$_{10}$, PM$_{2.5}$, and PM$_{10-2.5}$ has grown substantially in recent years. There are still more studies involving PM$_{10}$ than its fine and coarse components, but both size ranges appear to make similar contributions to the PM$_{10}$ associations.

Time-series studies of the associations between daily cardiovascular and pulmonary mortality and PM$_{10}$ were carried out in 29 European cities by Analitis et al. (2006). An increase in PM$_{10}$ by 10 μg/m$^3$ (lags 0 + 1) was associated with increases of 0.76% (confidence interval [CI]: 0.47–1.05%) in cardiovascular deaths and 0.58% (CI: 0.21–0.95%) in respiratory deaths.

In the first study to examine the roles of the chemical components of PM$_{2.5}$ on daily mortality, Laden et al. (2001) performed a source apportionment on the PM$_{2.5}$ in the Six Cities study and reported that the mobile-source component accounted, per 10 in PM$_{2.5}$, for a 3.4% (CI: 0.17–5.2%) increase in daily mortality, while the coal combustion source accounted for a 1.1% (CI: 0.3–2.0%) increase, while crustal materials were not associated with excess daily mortality.

Studies conducted in the past decade have examined associations between cardiac function and PM concentrations on the basis that PM-associated mortality and morbidity can be explained, at least in part, by alterations in cardiac autonomic balance, as measured by the heart rate variability (HRV). Associations were reported between decreased HRV and increased PM$_{2.5}$ in ambient air (Pope et al., 1999, 2004a,b; Gold et al., 2000; Creason et al., 2001; Holguin et al., 2003; Park et al., 2005; Schwartz et al., 2005). Riediker et al. (2004) reported that HRV was significantly associated with PM$_{2.5}$ concentration for young highway patrol troopers inside their patrol cars. While Gold et al. (2000, 2005) and Liao et al. (1999) found no such association for PM$_{10-2.5}$ in communities with low concentrations of PM$_{10-2.5}$, Lipsett et al. (2006) found that PM$_{10-2.5}$ and PM$_{10}$, but not PM$_{2.5}$, were associated with reduced HRV in a California community where PM$_{10-2.5}$ was higher than PM$_{2.5}$. Short-term increases in air pollution exacerbate existing cardiorespiratory disease...
leading to increased hospital admissions and, in some patients, to premature death (Peters et al., 2001). Recently, PM air pollution exposure was shown to be associated with exercise-induced myocardial ischemia in patients with coronary heart disease (Pekkanen et al., 2002) and in the rapid induction of acute myocardial infarction (Peters et al., 2001). In concordance with these short-term effects, the risk of mortality from cardiovascular disease is greater for those living in areas of greater pollution (Dockery et al., 1993; Pope et al., 2002), and the U.K. government has estimated that around 8000 excess deaths occur per annum as a result of air pollution.

Various studies in human populations exposed to ambient air PM have shown significant associations with cardiovascular effects, including defibrillator discharges (Peters et al., 2000), myocardial infarction (Peters et al., 2001), increased plasma fibrinogen (Pekkanen et al., 2000; Schwartz, 2001), ECG segment alterations (Pekkanen et al., 2002; Riediker, 2007; Yue et al., 2007), oxidative stress (Sorensen et al., 2005; Lanki et al., 2006), endothelial dysfunction (O’Neill et al., 2005), exercise-induced ischemia (Lanki et al., 2006), HRV (Chuang et al., 2007; Yeatts et al., 2007), elevated blood pressure (Ibald-Mulli et al., 2001; Auchincloss et al., 2008), blood lipids (Yeatts et al., 2007), flow-mediated dilatation (O’Neill et al., 2005; Schneider et al., 2008), von Willibrand factor and C-reactive protein (CRP) (Riediker, 2007; Yue et al., 2007), blood coagulability (Baccarelli et al., 2006), MS (Chen and Schwartz, 2008), emergency room visits (Sarnat et al., 2008), daily mortality (Lippmann et al., 2006; Franklin et al., 2008), and annual mortality (Laden et al. 2000; Pope et al., 2002; Hedley et al., 2002, 2004; Lipfert et al., 2006; Miller et al., 2007). The coherence of the effects seen in these studies with those seen in the human and animal PM inhalation studies is discussed in the next section.

**Chronic Exposures to Ambient Air PM**

Most of the evidence for adverse health effects from chronic exposure to PM is coming from prospective cohort studies of annual mortality rates in relation to long-term pollutant exposures in the Harvard Six Cities study (Dockery et al., 1993; Laden et al., 2006), the American Cancer Society (ACS) cohort (Pope et al., 1995b, 2002, 2004a,b), the Adventist Health Study on Smog (AHSMOG) study (Beeson et al., 1998), and the Veterans study (Lipfert et al., 2006) and are described in more detail in Chapter 3. The Six Cities and the ACS cohort studies are considered to have the greater strengths and are discussed most fully in the text that follows. The limitations of these key studies and the AHSMOG and Veterans studies are addressed in the text as well.

Dockery et al. (1993) reported on a 14- to 16-year mortality follow-up of 8111 adults in six U.S. cities in relation to average ambient air concentrations of TSP, PM$_{2.5}$, fine particle SO$_4^{2-}$, O$_3$, SO$_2$, and NO$_2$. Concentration data for most of these pollutant variables were available for 14–16 years. The mortality rates were adjusted for cigarette smoking, education, body mass index (BMI), and other influential factors not associated with pollution. The two pollutant variables that best correlated with total mortality (which was mostly attributable to cardiopulmonary mortality) were PM$_{2.5}$ and SO$_2$. The overall mortality rate ratios were expressed in terms of the range of air pollutant concentrations in the six cities. The rate ratios
(and 95% CIs) for both PM$_{2.5}$ and SO$_4$ were 1.26 (1.08–1.47) overall and 1.37 (1.11–1.68) for cardiopulmonary. The mean life shortening was in the range of 2–3 years.

The Dockery et al. (1993) study had the added strength of data on multiple PM metrics. The association became stronger as the PM metric shifted from TSP to PM$_{10}$. Within the PM$_{10}$, the association was much stronger for PM$_{2.5}$ than for the coarse component. Within the PM$_{2.5}$ fraction, both the SO$_4$ and non-SO$_4$ fractions correlated very strongly with annual mortality, suggesting a nonspecific response to PM$_{2.5}$.

Subsequent analyses of ACS data for more extended time periods (Pope et al., 2002) further substantiated the original findings and also provided much clearer, stronger evidence for ambient PM exposure relationships with increased lung cancer risk previously indicated for the AHSMOG study by Beeson et al. (1998).

It seems that the apparent association between long-term exposure to PM$_{2.5}$ pollution and mortality persists with longer follow-up as the participants in the cohort grow older and more of them die. In addition, the estimated PM$_{2.5}$ effect on cardiopulmonary and cancer mortality remained relatively stable even after adjustment for smoking status. The estimates were relatively robust against inclusion of many additional covariates: education, marital status, BMI, alcohol consumption, occupational exposure, and dietary factors. Education was an effect modifier, with larger and more statistically significant PM$_{2.5}$ effect estimates for persons with less education. Because this cohort has a much higher percentage of well-educated persons than the general public, the education effect modification suggests that the overall PM$_{2.5}$ effect estimates are likely underestimated by this study cohort as compared with that for the general public. A more extensive overview is given in Chapter 3.

**PRECLINICAL AND CLINICAL STUDIES**

To investigate the causal relationship between PM$_{2.5}$ and UFP and cardiovascular responses, several research groups have applied PM concentrator technologies to generate reasonably representative atmospheres of ambient air PM at elevated concentrations in the size ranges of interest (Sioutas et al., 1995, 1997; Kim et al., 2001; Demokritou et al., 2002, 2003). The equipment allows increased PM exposures in preclinical and clinical studies. Alternatively, collected PM fractions or surrogate mixtures, such as fly ash and diesel engine exhaust, have been used. A more detailed discussion on these studies is described in Part III of this book, and a few examples are described here.

In Chapel Hill, NC, controlled exposure of young, healthy adults to PM$_{2.5}$ caused an elevation in blood fibrinogen at 18 h post-exposure. This response was correlated with a Cu/Zn/V factor in the PM. In old, healthy adults, PM$_{2.5}$ exposures decreased HRV, a response not seen in the young adults. In young, healthy adults, PM$_{0.18}$ decreased HRV and increased D-dimer in the plasma; PM$_{2.5}$ increased polymorphonuclear leukocytes (PMNs) and monocytes in bronchoalveolar lavage (BAL) cells, decreased IL-8 in BAL fluid, and increased fibrinogen in plasma; and PM$_{10-2.5}$
increased PMN in BAL cells, decreased protein in the BAL fluid, decreased HRV, and increased the trend for clotting in the plasma (Ghio et al., 2000; Devlin et al., 2003; Samet et al., 2007).

In Los Angeles, young, healthy adults, as well as patients with asthma or chronic obstructive pulmonary disease (COPD), were exposed to PM$_{10-2.5}$, to PM$_{2.5}$, or to PM$_{0.18}$. PM$_{0.18}$ produced slight changes in mediators of blood coagulability and HRV in both normal subjects and asthmatics. Blood pressure decreased in asthmatics but increased in normal subjects. In healthy elderly subjects with COPD, there were reductions in pulse rate and frequency of ectopic beats, but there was no change in HRV after exposure to PM$_{2.5}$. In mild asthmatics exposed to PM$_{10-2.5}$, there were increases in heart rate but reductions in HRV. In both healthy normal subjects and mild asthmatics exposed to PM$_{2.5}$, there were reductions in O$_2$ saturation, forced expiratory volume (FEV)$_1$ 1 day later, and in low frequency HRV in both groups (Gong et al., 2003, 2004a,b, 2008).

In Toronto, there was a PM$_{2.5}$-related mean decrease in brachial artery diameter (BAD), but there were no changes in blood pressure in one study, while in a follow-up study involving most of the same subjects, PM$_{2.5}$ exposure produced a significant decrease in diastolic blood pressure. In both studies, the effects were significantly associated with OC. There were suggestive but no significant associations with EC and some metals (Cd, K, Zn, Ca, Ni) in the first study (Brook et al., 2002; Urch et al., 2004, 2005).

In Edinburgh, healthy and age-matched volunteers with stable coronary heart disease were exposed to PM$_{2.5}$ and to filter air. After PM exposure, there were increases in exhaled breath 8-isoprostane ($p < 0.05$), in blood flow, and plasma tissue plasminogen activator ($p < 0.005$), but there were no significant changes in markers of systemic inflammation and no effect on vascular function in either group of subjects (Mills et al., 2008). It was noted that most of the particulate mass consisted of sea salt, and far less PM was derived from combustion sources than were identified in the studies described above.

The still quite limited number of human PM inhalation studies has provided some provocative information on the ability of short-term PM inhalations to elicit statistically significant cardiovascular responses at concentrations approximating peak ambient levels in North America and Europe. These include responses to all three size ranges of current interest, in adults, and cover a wide range of ages and of preexisting health status. In most studies, there was an increase in plasminogen and a decrease in HRV. Furthermore, there is evidence that the chemical composition of the PM affected the responses. The extent to which the differences in PM composition among the different cities can account for the differences in responses in the studies summarized above remains to be determined.

A number of short-term inhalation preclinical studies using ambient PM have been performed with the use of concentrator technologies (Sioutas et al., 1997; Kim et al., 2001), but interspecies differences, genetically altered animal models for human diseases, and differing modes of inhalation that affect the inhaled dose complicate an overall view on the outcomes. In summary, inhaled urban PM$_{2.5}$ affected cardiac function in mice, rats, and dogs via oxidative stress, and the effects appear to be influenced more by inorganic PM components than by components associated
with secondary organic PM. At present, it is not clear how these outcomes can be interpreted in terms of risk for the general population or for specific groups at risk, such as people with compromised airways or an underlying cardiovascular disease. Even less is known on the effects of chronic exposure to PM$_{2.5}$. Subchronic exposures performed in Tuxedo, NY and in New York City (Lippmann et al., 2005a,b, 2006; Sun et al., 2005, 2008) and Columbus (Laing et al., 2009; Ying et al., 2009b) involved 10 weeks to 6 months of weekday inhalation exposures of mice and rats at mass concentrations of \(\sim 0.1 \text{ mg/m}^3\). These studies have produced a broad array of statistically significant cardiopulmonary responses, including increased and more invasive aortic plaque, vasomotor tone, vascular inflammation, macrophage infiltration, tissue factor expression, oxidative stress, increased blood pressure, exaggerated insulin resistance, and visceral inflammation/adiposity related to MS. Such a range of potentially serious health-related responses is remarkable, considering that the long-term average exposures of the animals to ambient air fine particles was only \(\sim 18 \mu\text{g/m}^3\) (30/168 \times 0.1 \text{ mg/m}^3). Some responses were greater in sensitive animal models, but some were seen in normal young animals. In addition, on a mass basis, diesel engine exhaust appeared to be less potent in inducing plaque development than corresponding exposures to concentrated PM$_{2.5}$, indicating that some components in ambient PM$_{2.5}$, which are not present in diesel engine exhaust, are responsible for the exacerbation of plaque progression (Quan et al., 2009). In most of these studies, biomarker assays that were performed on tissues from the animals exposed to PM$_{2.5}$ \textit{in vivo} have helped to clarify the mechanisms underlying the effects. Furthermore, the basic similarity of the responses to PM$_{2.5}$ in all three study sites suggests that the toxicity of ambient air PM$_{2.5}$ in the northeastern United States does not vary greatly. Since the PM$_{2.5}$ at the Tuxedo site has little locally generated mass, and is dominated by long-range transport, the effects may be largely due to the regional pollution.

**Coherence in Responses between Preclinical and Clinical Studies**

For short-term responses to PM in ambient air, a comparison can be made for short-term exposures of humans and laboratory animals exposed to PM by inhalation and to cellular responses \textit{in vitro} to aqueous suspensions of particle mixtures, such as ambient air PM, residual oil fly ash (ROFA), coal fly ash (CFA), and/or to individual PM components known to be present in ambient air. For chronic effects associated with long-term exposures to ambient air pollution, the most valid comparisons to effects observed in community-based populations are largely limited to those seen in laboratory animals receiving a long-term series of daily PM exposures. In this context, it is important to remember that people and animal models can differ substantially in their susceptibilities and sensitivities to PM exposures. For example, Wheeler et al. (2006) showed that, in response to ambient air PM exposures, people with COPD responded with increased HRV, while people with recent myocardial infarctions responded with decreased HRV, as did the normal healthy subjects in the PM inhalation studies cited in this chapter. In humans, most PM$_{2.5}$ inhalation studies reported increases in plasminogen and decreases in HRV, while in dogs and rats, most studies reported increases in
one or another index of oxidative stress, with two studies (one in rats and one in dogs) indicating decreased HRV. Variations in responses were attributable to differences in age, preexisting health status, and PM composition. In most of the cases where PM components were identified, the effects were more closely associated with inorganic, rather than with EC or OC. There were no chronic PM inhalation studies in humans. A series of subchronic PM inhalation studies have shown PM$_{2.5}$-related chronic, as well as acute, changes in HR and HRV (Chen and Hwang, 2005; Hwang et al., 2005), aortic plaque growth (Chen and Nadziejko, 2005), potentiated atherosclerosis (Sun et al., 2005), tissue factor expression (Sun et al., 2008), hypertension (Sun et al., 2008), MS (Sun et al., 2009), and vasomotor tone (Ying et al., 2009a).

**Coherence in Responses between (Pre-) Clinical and Epidemiological Studies**

The increases in plasminogen in PM$_{2.5}$-exposed humans was seen in humans in relation to ambient air PM$_{2.5}$ in NHANES III (Schwartz, 2001), while the decreases in HRV seen in human, dog, rat, and mouse PM$_{2.5}$ inhalation studies were seen in association with ambient air PM$_{2.5}$ in Helsinki (Pekkanen et al., 2002); Amsterdam, Helsinki, and Erfurt, Germany (Lanki et al., 2006); Taipei (Chuang et al., 2007); North Carolina (Riediker, 2007); and Erfurt (Yue et al., 2008). PM$_{2.5}$ PM exposure in an obese mouse model for 10 weeks caused insulin signaling abnormalities, providing a link between PM exposure and type 2 diabetes mellitus and MS (Sun et al., 2009). In the NHANES III population, Chen and Schwartz (2008) demonstrated a significant association between white blood cells (WBC) and PM$_{10}$, and a graded association between WBC and across subpopulations with increasing MS components. In a Chapel Hill, NC panel with type 2 diabetes mellitus, there were PM$_{2.5}$-related decreases in flow-mediated dilatation in BAD and small artery elasticity, and high levels of myeloperoxidase led to the strongest effects on endothelial dysfunction (Schneider et al., 2008). In greater Boston, four PM metrics were associated with decreased vascular reactivity in diabetics, with SO$_4^{2-}$ being associated with both decreased flow-mediated and nitroglycerin-mediated vascular reactivity, while black carbon was associated with only decreased flow-mediated vascular reactivity (O’Neill et al., 2005).

The other effects produced by long-term PM$_{2.5}$ inhalation studies in mice and rats, that is, increased deposition of plaque in the aorta, vascular inflammation, tissue factor expression, and blood pressure, are consistent with these factors being prevalent in human populations considered to be especially sensitive to the adverse effects of PM$_{2.5}$ exposures.

**The Role of PM Components**

Studies in which collected ambient air PM and specific mixtures containing components of ambient air PM were resuspended for controlled animal inhalation or lung instillation studies have produced results that can help interpret the biological plausibility of findings in the PM inhalation studies, and the PM components
that are especially influential. In an inhalation study in rats with Ni and V, Ni caused delayed bradycardia, hypothermia, and arrhythmogenesis at concentrations >1.2 mg/m³, while V alone did not induce any significant changes. However, when combined, Ni and V produced observable delayed bradycardia and hypothermia at 0.5 mg/m³, suggesting a synergistic relationship at high metal concentrations (Campen et al., 2001). However, these effects at very high concentrations of Ni and V do not necessarily support the associations of Ni with acute cardiac function changes at the very much lower Ni concentrations in the PM₂.₅ study in mice.

Intratracheal instillation studies involving lung exposures to dusts from the Utah Valley before, during, and after the strike, and ROFA dusts have been particularly informative because of well-established human health effects associated with the inhalation of these dusts. As discussed earlier in this chapter, the effects of ROFA and Utah Valley dusts have been attributed largely to their metals contents. This is consistent with the results of the intervention study in Hong Kong in which both monthly cardiovascular (and pulmonary) mortality rates dropped substantially after a mandated switch to low-S fuels and the associated step-function reduction in airborne Ni, V, and SO₂ (without any corresponding reduction in other metals or gaseous criteria pollutants) (Hedley et al., 2002, 2004). It is also consistent with daily peaks of Ni (but not V) and increased HR and decreased HRV in an atherosclerotic mouse model during the course of a 6-month PM₂.₅ inhalation study (Lippmann et al., 2006). On the other hand, there are clearly other PM₂.₅ components that confer cardiovascular toxicity. For example, Ottawa PM extracts instilled into rat lungs induced pronounced biphasic hypothermia, a severe drop in heart rate, and increased arrhythmias that were greater than those with the ROFA PM. No such effects were seen with a comparable instilled dose of Mt. St. Helens volcanic ash (Watkinson et al., 2000a,b). Furthermore, PM₂.₅ and PM₁₀-₂.₅ collected from six European cities with contrasting traffic profiles, PM composition, and in vitro analyses were instilled into spontaneously hypertensive (SH) rats. PM₂.₅ and PM₁₀-₂.₅ dose-related effects included blood viscosity, with a trend toward greater toxicity with increasing traffic levels. However, there was no correlation of any of the effect markers with combustion-exhaust-related polycyclic aromatic hydrocarbons (PAHs) except for an increase of lymphocytes associated with PM₂.₅ (Gerlofs-Nijland et al., 2007). An important role for metals is also evident in a study in which two tire dusts were instilled into the lungs of rats. TP1 was made from ground tires of recycled styrene butadiene rubber, while TP2 was from scrap tires. Tests were done with administered saline, TP1, TP2, soluble Zn, Cu, or both. At very high concentrations, the exposures induced cardiac oxidative stress (Gottipolu et al., 2008).

Aside from metals, there has been a considerable focus on motor vehicle exhaust as a source category that could account for the adverse health effects associated with PM₂.₅, and especially the soot in the exhaust from diesel engines. For acute responses, the most direct laboratory-based comparison of the effects of PM₂.₅ in ambient air and in diesel engine exhaust PM (DEP) can be found in papers by Cassee et al. (2002, 2005). They were able to produce acute increases in blood fibrinogen with both ambient air PM and with concentrated DEP, but it took far
higher concentrations of DEP than PM to do so. In terms of acute human responses, the situation is less clear. Mills et al. (2005) found acute exposure to DEP for 1 h at 300 μg/m³ did produce blood fibrinogen responses, while their PM₂.₅ exposures (Mills et al., 2008) did not. However, they noted that their ambient air PM (in Edinburgh, Scotland) was nearly all sea salt. Human PM₂.₅ exposures in Chapel Hill, Los Angeles, and Toronto, at concentrations well below 300 μg/m³, did produce cardiac system responses.

The recent studies in which the cumulative effects associated with subchronic inhalation exposures to ambient air PM₂.₅ were directly compared in the same animal models and exposure durations to those of other complex toxicant mixtures, such as diluted diesel engine exhaust (Quan et al., 2009) and sidestream cigarette smoke (Chen et al., 2009), were especially informative. They showed that eastern U.S. regional PM₂.₅ was considerably more atherogenic than either diesel exhaust or sidestream smoke on the basis of PM mass inhaled, even without consideration of the gaseous toxicants associated with the sidestream smoke and diesel exhaust particles.

Overall, it appears that the cardiovascular effects of ambient air PM₂.₅ are greatly influenced, if not dominated by their metal contents, especially the transition metals, and that Ni is likely to be a key component.

**Current Knowledge Gaps on the Health Effects of PM**

While there is mounting evidence that excess daily mortality, morbidity, and cardiac function are associated with short-term peaks in PM₁₀ and PM₂.₅ pollution, the public health implications of this evidence are not yet fully clear. Key questions remain the following:

- Which specific components of the PM₂.₅ and PM₁₀₋₂.₅ are the most influential in producing the responses?
- Do the effects of the PM depend on co-exposure to irritant vapors, such as O₃, SO₂, or NOₓ?
- What influences do multiple-day pollution episode exposures have on daily responses and response lags?
- Does long-term chronic exposure predispose sensitive individuals to being “harvested” on peak pollution days?
- How much of the excess daily mortality is associated with life shortening measured in days or weeks versus months, years, or decades?

The results of studies in recent years have made it possible to frame the remaining unresolved issues in a more coherent and focused manner. This book has put its focus on ultrafine particles and effects on the cardiovascular system. Part I describes the current knowledge on the epidemiological evidence. Epidemiological studies usually associate air pollution measurements at a fixed station with health effects of the population living in a large area around this station, irrespective of the wind directions or other factors that influence personal exposure. Part II is therefore dedicated to the relationships among air quality mea-
surements, dispersion, and personal exposure, and between personal exposure and internal dose. After particles are deposited in the airways and the lung, ultrafine insoluble particles are likely to escape defense mechanisms such as phagocytosis by macrophages, passing the barrier between the alveolar spaces and the blood, and reaching the systemic circulation. This process, referred to as translocation, plays a major role in the development of cardiovascular health effects. Since epidemiology will not be able to either unravel underlying biological mechanisms (mainly due to a lack of sufficient and relevant data) or detect what part in the complex PM mixture is causing what type of effect, cell cultures (in vitro), experimental in vivo animal (preclinical), and human (clinical) studies are performed (Part III). This section also acknowledges the fact that “mass” is a crude parameter to relate PM air pollution to health effects and that chemical composition will play an important role in the development or boosting of toxic responses. Studies on cardiovascular health effects due to exposure to PM$_{2.5}$ and UFP form the major part of this book and are presented in Part IV. The last part (Part V) summarizes the environmental and public health policy and also links ambient air pollution with a relatively new area for which overlap can be expected, that is, nanotechnology.

One key unresolved issue is the role of SO$_4^{2-}$ and why it consistently correlates with mortality and morbidity as well as, or better than, other metrics of PM pollution. It is extremely unlikely that SO$_4^{2-}$, per se, is a causal factor. If it is not, then it must be acting as a surrogate index for one or more other components in the PM mixture.

One possibility is that the effects are really due to the PM$_{2.5}$ mass, irrespective of particle composition, and that SO$_4^{2-}$ is a more stable measurement of airborne PM$_{2.5}$ than is the reported PM$_{2.5}$ itself. The ambient PM$_{2.5}$ includes semivolatile compounds, such as nitrates (primarily ammonium nitrate) and organics formed by photochemical reactions in the atmosphere. There can be considerable volatilization of these species on sampling filters, resulting in negative mass artifacts whose magnitude varies with source strengths and ambient temperature. Some of the semivolatile organics may account for the associations reported between indices of traffic-related pollution and health effects.

Another possibility is that SO$_4^{2-}$ is serving as a surrogate for H$^+$, a more likely active agent on the basis of the results of controlled exposure studies in humans and animals.

A third possibility is that the causal factor is the number concentration of irritating particles, which would be dominated by the particles in the ultrafine mode (diameters below 50 nm) (Oberdörster et al., 1995). Epidemiological support for this hypothesis has been provided by Peters et al. (1997), who reported closer associations between peak expiratory flow rates (PEFRs) and symptoms in adult asthmatics with particle number concentration than with fine particle mass concentration in Erfurt, Germany.

A fourth possibility is that soluble transition metals in the ambient PM generate sufficient amounts of reactive oxygen species (ROS) in the respiratory tract airways to cause inflammatory responses and chronic lung damage (Huang and Ghio, 2006).
A fifth possibility has been proposed by Friedlander and Yeh (1996), that is, that reactive chemical species, such as peroxides, are responsible for the health effects associated with fine particles, and that $\text{SO}_4^{2-}$, being a product of chemical reactions involving hydrogen peroxide, is serving as a surrogate measure of the airborne peroxides. Support for this hypothesis has been provided by an in vivo animal exposure study by Morio et al. (2001).

It is also possible that effects are related to a hybrid of $\text{H}^+$ and ultrafines, that is, acid-coated ultrafine particles. Sulfuric acid coatings on ultrafine zinc oxide particles produce about the same responses as pure sulfuric acid for a given number of equivalent-sized particles, yet the coated particles only had one-tenth of the acid content per unit volume of air. Thus, the response may be related to the number of acidic particles that deposit on the lung surfaces, rather than the amount of acid deposited. In other words, the total concentration of $\text{H}^+$ may be a better surrogate of the active agent than $\text{SO}_4^{2-}$ or PM$_{2.5}$, but it is still a crude index for the number concentration of irritant particles. Amdur and Chen (1989) suggested that number concentration was important for sulfuric acid aerosol, and Hattis et al. (Hattis et al., 1987, 1990) gave the concept a name, that is, “irritation signaling.” Research of Chen et al. (1995) indicated that acid-coated particles much smaller than those discussed by Hattis et al. (Hattis et al., 1987, 1990) were capable of producing lung responses.

If the number concentration of acid-coated particles is the most relevant index of the active agent in ambient PM, then new sampling techniques will be needed to characterize ambient air PM concentrations and personal exposures.

Other components of UFP have not been well characterized either, and they may also be important health stressors. One class is the volatile trace metals (such as As, Cd, Cu, Ni, Pb, V, Zn), which condense as UFP in the effluent airstream of fossil fuel combustors (Amdur et al., 1978) and are inefficiently captured by air cleaners for fly ash collection. Another class is the ultrafine organics from atmospheric photochemical reaction sequences.

Any remaining inconsistency between the epidemiological findings and the results of the controlled exposure studies may be explicable on the basis that the relatively rare individuals who respond in the epidemiological populations are an especially responsive subset of the overall population, and the low probability that such sensitive individuals would be included in the controlled exposure studies in the laboratory. An alternative hypothesis is that the controlled exposure atmospheres have not contained the highly toxic components or ultrafine particle sizes that may be present in ambient atmospheres.

In summary, excess daily mortality and morbidity have been related to ambient PM at current levels in many communities in the United States and around the world using available pollutant concentration data. However, it is not at all clear whether any of the pollutant indices used are causally related to the health effects or, if none of them are, which is the best index or surrogate measure of the causal factor(s). This gap can best be addressed by analyses of pollutant associations with mortality and morbidity in locations where a number of different pollutant metrics are available simultaneously, using analytic methods not dependent on arbitrary model assumptions.
REFERENCES


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