The Health Relevance of Ambient Particulate Matter Characteristics: Coherence of Toxicological and Epidemiological Inferences

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The aim of this article is to review progress toward integration of toxicological and epidemiological research results concerning the role of specific physicochemical properties, and associated sources, in the adverse impact of ambient particulate matter (PM) on public health. Contemporary knowledge about atmospheric aerosols indicates their complex and variable nature. This knowledge has influenced toxicological assessments, pointing to several possible properties of concern, including particle size and specific inorganic and organic chemical constituents. However, results from controlled exposure laboratory studies are difficult to relate to actual community health results because of ambiguities in simulated PM mixtures, inconsistent concentration measurements, and the wide range of different biological endpoints. The use of concentrated ambient particulates (CAPs) coupled with factor analysis has provided an improved understanding of biological effects from more realistic laboratory-based exposure studies. Epidemiological studies have provided information concerning sources of potentially toxic particles or components, adding insight into the significance of exposure to secondary particles, such as sulfate, compared with primary emissions, such as elemental and organic carbon from transportation sources. Recent epidemiological approaches incorporate experimental designs that take advantage of broadened speciation monitoring, multiple monitoring stations, source proximity designs, and emission intervention. However, there continue to be major gaps in knowledge about the relative toxicity of particles from various sources, and the relationship between toxicity and particle physicochemical properties. Advancing knowledge could be facilitated with cooperative toxicological and epidemiological study designs, with the support of findings from atmospheric chemistry.

Although ambient air particulate matter (PM) has been clearly associated with adverse human health outcomes (NRC, 2004; U.S. EPA, 2004), the relationship between specific physicochemical properties of PM and these health effects remains largely unresolved. One of the major barriers to continued advancement in this regard has been the lack of a comprehensive integration of current knowledge derived from three different disciplines, namely, atmospheric chemistry, toxicology, and epidemiology. In fact, the current (U.S.) National Ambient Air Quality Standards (NAAQS) for PM are founded on a long
history of often divergent research in these areas. While based on mass concentration as the exposure metric and while chemically nonspecific, the NAAQS does recognize discrete particle size modes as factors influencing health outcomes.

Over the past decade, attempts to provide linkages between health effects and ambient PM properties have increased. These include accounting for a refined differentiation of particle size by number concentration and specific area per unit mass as well as by chemical composition. The aim of many contemporary epidemiological and toxicological studies is to determine the toxicity of specific classes of airborne particles, providing an improved basis for regulation of PM. This goal has been facilitated by sustained measurements of fine PM mass concentration and composition, for example, in the U.S. Environmental Protection Agency (EPA) speciation network.

The search for PM-specific effects has been difficult in the context of a complex mix of particulate and gaseous air pollutants, especially since the latter may have biologically plausible associations with various health end points that are also potentially related to PM. Some of the strongest epidemiological evidence on associations between PM and both mortality and morbidity highlights the complexities of disentangling effects of  specific components of these pollutant mixtures (Krewski et al., 2000; Gauderman et al., 2004).

This article takes an interdisciplinary approach to the interpretation of results from health effects studies of PM. It attempts to provide an integration of results reported, largely between the mid-1990s through mid-2005, in both the epidemiological and toxicological fields, so as to provide a framework for the relationship between physicochemical properties of PM and health effects. As such, the article complements the recent U.S. EPA PM Criteria Document (U.S. EPA, 2004), which focuses largely on the relationship solely between PM mass concentration and health outcomes.

The discussion in this article considers the following three questions:

1. What types or classes of PM, or their constituents, are most harmful to human health?
2. Can the sources of PM that contribute to harmful exposures be determined?
3. What are the methodological limits, data constraints, coexposures, differential susceptibilities, or other factors that bound our knowledge?

Following an introductory summary of PM characteristics, the starting point for this evaluation is guidance as to possible health impacts provided by toxicological studies. This is followed by a discussion of recent epidemiological studies that have improved our knowledge about properties and sources of PM that may be relevant to adverse health outcomes. At this point, it is important to understand that when links between specific sources and health effects are made, such associations can only be “validated” for the time period being evaluated by the study. This is because, very often, specific emissions from sources can vary with time due, for example, to changes in fuel sources or industrial processes. However, results from epidemiological studies associating sources with effects can provide useful information on potential components or properties of PM that may be involved in adverse health outcomes knowing the specific properties of PM released from the sources at the time of the study evaluation. The final section of the article discusses the coherence of evidence between disciplines that may allow for determination of the relationship between PM properties, sources, and health outcomes. Some suggestions for further exploitation of new “integrated” designs for future studies are noted.

**ATMOSPHERIC PARTICULATE MATTER**

Historically, health effects communities have faced formidable barriers to understanding the significance of ambient PM exposure, due to the highly complex nature of atmospheric aerosols and to their various sources of origin. Ambient PM is generally categorized in terms of various cumulative size modes, as follows: “thoracic particles,” those less than 10 µm aerodynamic diameter (PM$_{10}$); “fine particles,” those less than 2.5 µm aerodynamic diameter (PM$_{2.5}$); “coarse particles,” those between 10 µm and 2.5 µm (PM$_{10-2.5}$); and “ultrafine particles,” those less than 0.1 µm diameter. A differentiation by size-based mass concentration and resultant broad differences in chemical composition within each mode has led to the adoption of two size groups for regulatory purposes in the United States, namely, PM$_{2.5}$ and PM$_{10}$.

Ambient PM derives from a variety of sources. PM generally can be divided into primary PM that is directly emitted into the atmosphere from a source, and secondary PM that results from atmospheric chemical reactions of precursor gases. Natural sources for PM are identified largely with blowing soil dust, sea salt, geological disturbances, biological debris, and oxidation of biogenic reactive gases. Anthropogenic particle and reactive precursor gas sources include fossil fuel combustion from stationary and transportation sectors, fugitive emissions, and industrial, commercial, and residential activities.

Monitoring of particle mass concentration (in terms of total suspended particles, TSP) first began in the United States with the National Air Surveillance Network (NASN) in a few cities. These measurements provided guidance to health scientists, who could address not only TSP, but also specific chemical constituents, such as lead from combustion of gasoline, sulfate as a marker for fossil fuel combustion, and benzene-soluble organics containing a class of carcinogens, namely, polycyclic aromatic hydrocarbons (PAH).

In the 1970s, research on aerosols allowed a description of particle size distributions for different sources and “aged”

* Aerosols are rigorously defined as a suspension of solid or liquid particles within a gaseous medium. However, consistent with contemporary usage in environmental studies, this article refers to aerosols principally in terms of the suspended particle component.
ambient conditions (Whitby & Sverdrup, 1980). At this time, a much improved understanding of the nature of bulk inorganic and organic components of particles became available (Hidy et al., 1980). While the complex character of PM was recognized, the focus remained on selected monitored properties, most notably sulfate.

PM air monitoring in the United States has evolved with measurements of mass concentration and composition over limited time periods, and resulted in efforts to assess PM$_{10}$ (in the 1980s), PM$_{2.5}$ (after 1997) with the Federal Reference Method (FRM), and bulk chemical composition to facilitate estimates of a composition-mass balance (Federal Speciation Network, after 1999). While research efforts since 1970 have resulted in a complex picture of PM chemistry, the focus of toxicological as well as epidemiological studies remained on size-differentiated fraction, but not by component. For example, regions such as the eastern United States are strongly influenced by organic carbon and ammonium salts of sulfate, while major parts of California are dominated by nitrate and organic carbon. Arid regions contain increased amounts of soil dust, while agricultural regions associated with ammonia emissions often experience elevated nitrate concentrations (NARSTO, 2004).

Included in Table 1 is an index for past epidemiological and toxicological studies relevant to ambient aerosols. From a public health point of view, the improvement in knowledge about sources of PM and the complex chemical nature of PM place new requirements on the diversity of the design and execution of toxicological studies. In the case of organic species, for example, more than 200 compounds have been identified in various classes, including alkanes, alkenes, aromatics, PAH, oxygenated compounds (including aldehydes, ketones and carboxylic acids), amino compounds, and nitrates (Seinfeld & Pandis, 1998). Of these species, investigators are attempting to identify a practical subset of compounds of interest for potency and concentration for toxicological consideration. Further- more, PM is rarely present in pure physical or chemical form. The physicochemical conditions of particles vary widely with source and age of the particles, such that crystals, polycrys- talline solids, porous spores, agglomerates, and liquid droplets have been sampled. Chemical constituents can be internal or on the particulate surface, with a core and a shell having different compositions. Low-molecular-weight gaseous material, such as formaldehyde or acetaldehyde, can be adsorbed onto particle surfaces and, thus, become available for biological interaction.

Given the diverse characteristics of atmospheric PM, including its variation in space and time, determining health consequences in a relatively simple manner is a formidable task. The discussion of contemporary toxicology and epidemiology in the following sections shows how far we have progressed.

**TOXICOLOGICAL INFERENCEs FOR HEALTH EFFECTs**

The diversity of PM properties that may be relevant to public health results in a potentially large and complex matrix for experimental investigation. This section provides an overview of biological plausibility for toxicity of PM physicochemical properties, based upon controlled exposure studies. These studies have used ambient PM surrogates as well as “real world” concentrated ambient PM (CAPs). The aim is to indicate those specific characteristics that may be potentially important in affecting public health based upon biological responses that may underlie outcomes noted in epidemiological studies of PM. Potential particle–gas interactions in modulating biological responses to PM are not discussed.

The advantage of controlled studies is that they provide the ability to evaluate directly the influence of various factors on response without the complication of confounding variables inherent in epidemiological studies. By allowing precise control over critical variables, namely particle size, exposure concentration, and exposure duration, they can establish cause–effect relationships for specific materials and can be used as a basis to develop actual dose-response profiles. Toxicology can provide needed mechanistic support to epidemiological evidence to strengthen the scientific arguments for a specific particle concentration and/or exposure duration as being critical for initiation of a response of interest. Toxicology can also provide validation of coherent mechanisms underlying the evidence on which epidemiological conclusions are based, thus providing a margin of confidence in these conclusions.

One of the difficulties in attempting to assess properties of PM in terms of their relative contribution to toxicity is that observed biological effects may often differ between studies. This may be due to the use of varied endpoints, to different exposure concentrations, different biological models, and exposures that are not comparable to each other due to the manner in which the PM was generated, collected, or used (Singh et al., 2004). Not only can effects on a specific biological endpoint differ as a function of PM characteristics, but specific types of PM can affect some endpoints and not others (Seagrave et al., 2002). Furthermore, the “state” of the biological exposure system may also play a role in this regard. For example, it has been observed that different PM-associated components differentially affected alveolar macrophages depending on the activation state of these cells at the time of exposure (Imrich et al., 2000). Thus, the total experimental “model” used, in terms of both PM and biological system, will determine the “message” received.

*Organic carbon is known to have ambiguities in semi-volatile species (SVOC) that can adsorb onto particles and filter media. The SVOC component is not captured quantitatively by all sampling methods.
TABLE 1
Comparison of health studies and bulk composition of urban fine particles (PM$_{2.5}$) in the United States

<table>
<thead>
<tr>
<th>Measure or constituent</th>
<th>Concentration range ($\mu g/m^3$)</th>
<th>Major sources</th>
<th>Epidemiology studies$^a$</th>
<th>Toxicology studies$^a$</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mass$^b$</td>
<td>4–25</td>
<td>—</td>
<td>X</td>
<td>X</td>
<td>Increased interest in ultrafine particles recently</td>
</tr>
<tr>
<td>Sulfate$^c$</td>
<td>1.5–6</td>
<td>Fuel combustion</td>
<td>x</td>
<td>X</td>
<td>Sulfate is identified mainly with ammonium salts</td>
</tr>
<tr>
<td>Nitrate</td>
<td>0.5–5</td>
<td>Fuel combustion</td>
<td>x</td>
<td>x</td>
<td>Nitrate is identified mainly with ammonium salts</td>
</tr>
<tr>
<td>Acidity</td>
<td>0.01–&lt;0.2</td>
<td>Secondary sulfate or nitrate</td>
<td>x</td>
<td>x</td>
<td>Acidity in the atmosphere varies from acid salts to strong acids; the latter are highly transient in the air.</td>
</tr>
<tr>
<td>Metal salts or oxides</td>
<td>&lt;0.1–2</td>
<td>Soil dust, road dust; and industrial processes</td>
<td>x</td>
<td>x</td>
<td>Soil dust components are believed to be mainly oxides; industrial metals vary as oxides or salts</td>
</tr>
<tr>
<td>Black or elemental carbon (EC)$^d$</td>
<td>1–2</td>
<td>Fuel combustion</td>
<td>x$^h$</td>
<td>x$^f$</td>
<td>Black carbon in the atmosphere is not truly elemental in nature but is likely to be a mix of elemental material and oily char from combustion</td>
</tr>
<tr>
<td>Organic matter (OM)$^{d,e}$</td>
<td>1–6</td>
<td>Fuel combustion; industrial and biological material</td>
<td>x$^b$</td>
<td>x$^f$</td>
<td>The operationally defined differentiation of EC and OC is ambiguous, but is the key measure of both components in monitoring</td>
</tr>
<tr>
<td>Other unidentified$^g$</td>
<td>0.5–4</td>
<td>—</td>
<td></td>
<td></td>
<td>From closure of chemical mass balance</td>
</tr>
</tbody>
</table>

Note. The listed composition includes a typical range of annual average ambient concentration components that are estimated to provide a reconstructed particle mass balance.

$^a$Large number of studies (X); small number of studies (x).

$^b$Mass reported is based on the FRM filter method, which does not account accurately for semivolatile components, including nitrate and SVOC. These may be a factor in exposure, but have not been investigated.

$^c$Sulfate derives from primary emissions of acidic material associated with metals such as Fe, Ni, and V from fossil fuel combustion such as residual oil, and secondarily from oxidation of sulfur dioxide emissions in the atmosphere. The former is believed to be a minor (<5%) fraction of total PM-associated sulfate.

$^d$Black and organic carbon monitored in United States and elsewhere only after 1999. The measurement method is operationally defined in terms of a differential response to heating of filter samples.

$^e$By convention, OM is given as 1.4 $\times$ organic carbon concentration. The factor of 1.4 actually is believed to be variable depending on the age and mix of sources of OC. Includes biological debris, e.g., fine particle bacteria, virus, detritus, waxy material, etc.; also includes a large number of chemical species from primary and secondary sources, of which only perhaps 20–25% by mass have been identified.

$^f$Organics investigated to date focused mainly on diesel exhaust particles, PAH, and biological indicators such as endotoxin.

$^g$Believed to include adjustment for organic matter, bound water, chlorides, and other salts, as well as uncertainties in metal compound composition.

$^h$A few epidemiological studies have inferred a relationship to carbon through traffic proximity studies, for example, and identification with transportation using a Pb marker for gasoline.
The toxicity of PM may be due merely to the particle’s presence on biological tissue, to its chemical constituents (including any adsorbed surface components) or to some combination of these factors. Toxicological evaluations have examined a number of PM physicochemical characteristics in relation to their potential for production of adverse biological effects. In their final report, the NRC Committee on Research Priorities for Airborne Particulate Matter (NRC, 2004) provides a summary table of PM characteristics that may be important to health responses. These include the following: size mode; mass concentration; number concentration; acidity; particle surface chemistry; particle core chemistry; metals; carbon (organic carbon [OC], and black or elemental carbon [EC]); biogenic origin; secondary inorganic aerosols; and material associated with the earth’s crust. Other characteristics that have been recognized as potentially playing a role in toxicity are particle surface area, chemical reactivity, water solubility of constituent chemicals, and geometric form of the particles. This listing, of course, is based on those characteristics that have undergone the most scrutiny by investigators in the field.

**Particle Size Mode as a Modulator of PM Toxicity**

Evaluation of size mode per se as a modulating factor in PM toxicity is difficult since it is not independent of chemical composition; that is, certain size modes tend to contain certain chemical components. Furthermore, there are clear differences between particles in different size modes in terms of total and regional dosimetry within the respiratory tract, and subsequent pathways and rates of translocation both within and outside of the respiratory tract. It is often difficult to separate effects due to dosimetry from effects due to other characteristics of the particles. For example, in a study using different size modes of the same chemical material, the adverse effects of ultrafine and fine particles were comparable when assessed in terms of deposition doses; however, since the deposition efficiency of the ultrafine particles was higher, their toxicity may actually have been greater than that for the fine particles when considering mass concentration as the exposure metric (Takenaka et al., 2004). It has been suggested (Seaton & Dennekamp, 2003) that the respiratory tract may actually be more sensitive to particle number than to particle mass.

The issue of the “correct” or “relevant” exposure metric to use in evaluation of health outcomes is quite important. For example, rats exposed to ultrafine carbon showed no evidence of a pulmonary inflammatory response, but showed extrapulmonary effects, including changes in the number of blood neutrophils, and alteration of plasma thrombin-antithrombin complex or fibrinogen levels (Elder et al., 2004). However, as previously noted, for a given mass concentration, an atmosphere containing ultrafine particles will have a greater reactivity of the original material (Pan et al., 2004). However, it has been observed that the coarse and fine fractions of PM were equally effective in the generation of inflammatory mediators, and that effects were greater than that due to carbon black, suggesting that chemicals adsorbed onto the particle surface, rather than the mere presence of the particle itself, can be responsible for toxicity (Pozzi et al., 2003).

The difficulty in attempting to determine the relative role of size versus chemistry is quite evident from studies using concentrated ambient particles (CAPs). For example, concentrated coarse and fine particles from air in Southern California, when used to expose cells in vitro, resulted in different extents of oxidative stress response that was related to specific chemical components that differed in relative concentration within each fraction (Li et al., 2002b). Similarly, and using CAPs from ambient air in Los Angeles, there appeared to be enhanced toxicity of ultrafine compared to fine particles in terms of generating redox activity that correlated with the OC and PAH composition of these two size modes (Li et al., 2003).

Ultrafine particles may be a size mode whereby actual physical size, rather than chemical composition, is the specific particulate property responsible for toxicity. These particles seem to produce a more significant pulmonary inflammatory response than that produced by fine particles having the same chemical composition and at the same exposure mass concentration (Oberdörster et al., 1992; Li et al., 1996, 1997, 1999). However, as previously noted, for a given mass concentration, an atmosphere containing ultrafine particles will have a greater number concentration than will one consisting of fine particles. Thus, if response is the result of the number of particles depositing per unit time, then dose would actually be greater for ultrafines than for fines. Furthermore, ultrafine particles have a greater total surface area available for adsorption of toxic chemicals.

An enhanced biological effect from ultrafine particles may relate to systemic health outcomes found in epidemiological studies. For example, rats exposed to ultrafine carbon showed no evidence of a pulmonary inflammatory response, but showed extrapulmonary effects, including changes in the number of blood neutrophils, and alteration of plasma thrombin-antithrombin complex or fibrinogen levels (Elder et al., 2004). However, the investigators could not conclude whether the observed effects were size or chemical specific. Similarly, rats exposed to ultrafine carbon particles showed increased heart rate and decreased heart-rate variability, but no indication of an inflammatory response and no change in the expression of genes having thrombogenic relevance (Harder et al., 2005).
A potential mechanism for enhanced effects of ultrafine particles may be more effective translocation from the respiratory tract to extrapulmonary sites as compared to larger particles. For example, ultrafine EC particles inhaled by rats were found in brain tissue, and were postulated to reach there via translocation along the olfactory nerve following deposition on the olfactory mucosa of the nasopharynx (Oberdörster et al., 2004). This pathway circumvents the protective blood brain barrier of the central nervous system, and provides a direct route for inhaled PM into the nervous system without transport via the systemic circulation. Similarly, ultrafine gold particles instilled intranasally were found to translocate along the axons of the olfactory nerves to the olfactory bulb (DeLorenzo, 1970). A comparable pathway for translocation of soluble transition metal compounds has also been postulated (Tjalve & Henriksson, 1999; Arvidson, 1994; Dorman et al., 2002). Such a pathway may not be limited to ultrafine particles, since soluble manganese particles in the 1–2 µm size range appeared to translocate to the brain following inhalation exposure (Dorman et al., 2004).

Ultrafine particles also have been found to translocate from the respiratory tract to liver, although the extent of such translocation appears to vary in different studies using different species (Brown et al., 2002; Oberdörster et al., 2002; Kreyling et al., 2002). This pathway circumvents the protective blood liver barrier of the general liver system, and provides a direct route for inhaled PM into the liver system without transport via the systemic circulation. Similarly, ultrafine gold particles instilled intranasally were found to translocate along the axons of the olfactory nerve to the olfactory bulb following deposition on the olfactory mucosa (DeLorenzo, 1970). A comparable pathway for translocation of soluble transition metal compounds has also been postulated (Tjalve & Henriksson, 1999; Arvidson, 1994; Dorman et al., 2002). Such a pathway may not be limited to ultrafine particles, since soluble manganese particles in the 1–2 µm size range appeared to translocate to the brain following inhalation exposure (Dorman et al., 2004).

Ultrafine particles may have an enhanced ability to induce cellular damage by differentially affecting cellular organelles. Concentrated ultrafine ambient air particles were found to engage in subcellular penetration, thus gaining direct access to intracellular targets, with potential for enhanced toxicity (Geiser et al., 2005). For example, ultrafine particles resulted in mitochondrial damage to a greater extent than did fine particles obtained from the same geographical region in one study (Li et al., 2003). An enhanced ability of ultrafine particles to effectively translocate outside of the lungs or to enter cells may result in responses occurring sooner after exposure than would be seen with larger particles (Ramage et al., 2004).

Ideally, attempts to compare effects due to size mode should use PM from the same geographical area. Huang et al. (2003) exposed human bronchial epithelial cells to extracts of particles collected from Taiwan ambient air in three size ranges: PM<sub>1.0</sub> (<1 µm diameter), fine particles, and coarse particles. The ability of PM to elicit inflammatory cytokine production and to cause lipid peroxidation was found to be dependent on particle size, being most evident for the ultrafines. The relation between response and specific chemical components was less definite, suggesting that the observed responses were associated either with different sets of particle components within each size mode or with nonspecific size effects. This study thus tends to suggest that effects of specific particle components can only be determined if a study is restricted to a single particle size range.

In a similar comparative study, using particles collected by ambient concentrators in the Los Angeles area, Li et al. (2003) examined differences in size and composition between ultrafine, fine, and coarse particles in relation to uptake by macrophages and epithelial cells, and their ability to induce oxidative stress. On a mass basis, the ultrafine particles were more potent than either the fine or coarse modes in this regard. However, as already described, it was not clear whether observed effects were due to particle size alone or to chemistry, in that the ultrafine mode would have a higher number concentration and greater surface area per unit mass for potential adsorption than would the larger size modes. More recently, asthmatic and healthy adults exposed to CAPs in which 80% of the mass was coarse and the rest was <2.5 µm showed increases in heart-rate and decreases in heart-rate variability (Gong et al., 2004). Thus, coarse PM may have affected the autonomic nervous system to some extent in this study.

In summary, current evidence provides only an equivocal answer to the question of a nonspecific role for PM in modulating toxicity. As noted, it is difficult, if not impossible, to separate size from other characteristics, such as chemical composition, number concentration, or surface area. Even solubility may play a role in this regard, and solubility is another physical factor that differs between different particle size modes. For example, PM fractions <2.5 µm showed greater solubility and metal release than did fractions >2.5 µm (Smith et al., 1998). Furthermore, the specific bioactivity of ambient PM may actually depend on the relative proportion of soluble versus insoluble mass in the exposure atmosphere (Imrich et al., 2000). For example, when PM was collected from various sites and tested for adjuvant activity, the water-insoluble fraction was generally more potent than the water-soluble fraction (Steerenberg et al., 2005). Thus, on a number of counts, it is difficult to separate size from chemistry in attempting to determine PM characteristics that may relate to adverse health outcomes.

**Chemical Composition as a Modulator of PM Toxicity**

There is ample evidence suggesting that specific chemical properties of PM link with biological response. As an example, human alveolar macrophages were incubated with fine PM that had been subjected to various procedures, including organic solvent extractions, high-temperature heating, and acid digestion, processes that changed the surface characteristics of the original material (Obot et al., 2004). The results showed that PM toxicity was dependent on the surface characteristics of the particles, in that alterations in cell viability differed with the different extractions. PM subjected to acid digestion, which removed metallic and organic components, or treated with cyclohexane, which separated polar from nonpolar organic compounds, produced no change in viability. On the other hand, viability was reduced with untreated PM and heat-treated PM (which had decreased OC content).
As noted, various specific chemical components of PM have been targeted for study in terms of providing plausibility for health outcomes derived from epidemiological studies. The following subsections discuss evidence for toxicity of these chemical constituents, independent of other potential modulating factors.

**Elemental and Organic Carbon**

A large fraction of ambient PM in many areas is derived from combustion processes and therefore contains significant amounts of carbon, as both EC and OC. Either or both may be contributory to PM-related health outcomes. For example, both the organic and elemental carbon components of CAPs were associated with changes in brachial artery diameter in young healthy adults (Urch et al., 2004; Brook et al., 2002). An association between elevated indices of oxidative stress in plasma and carbon black, which generally consists of a mixture of partially combusted hydrocarbons, has been noted (Serensen et al., 2003), as was an association between carbon black exposure and altered heart-rate variability (Tankersley et al., 2004). Lipid peroxidation in human bronchial epithelial cells was found to be correlated with both the EC content and OC content of CAPs collected in Taiwan (Huang et al., 2003).

In spite of the fact that OC can comprise a substantial portion of the mass of ambient PM in most locations, there has been little examination of effects from specific OC components on health outcomes related to PM. This is due to the fact that the organic fraction of ambient PM is quite heterogeneous and not well characterized in most geographical settings. However, studies with DEP, as well as some other OC particles, have shed light on the potential toxicity of groups of OC components.

Li et al. (2002a), using an in vitro assay, showed that DEP and concentrated PM10 and PM2.5 induced oxidative stress in alveolar macrophages, a response found with the particulate-associated organic fraction and, especially, for particles highest in PAH. Organic chemicals adsorbed on the surface of some ultrafine particles have been shown to mimic the effects of intact particles in assays assessing mitochondrial damage and production of reactive oxygen species (ROS) (Hiura et al., 1999, 2000). Such effects can also be reproduced by functionalized aromatic and polar chemical groups fractionated from DEP (Alsberg et al., 1985; Li et al., 2002b). These compounds are relevant because aromatic fraction is enriched in PAH, whereas the polar fraction contains several oxo-PAH compounds, including quinones. Quinones are able to redox cycle and produce ROS, whereas PAH can be converted to quinones by cytochrome P-450, epoxide hydrolase, and dihydrodiol dehydrogenase (Penning et al., 1999); thus, quinones may be involved in PM-induced oxidative stress (Monks et al., 1992; Penning et al., 1999). Some effects of DEP in terms of the ability to generate ROS may be inhibited by chemicals that reduce quinones to hydroxy derivatives, also suggesting that quinones or oxidized PAH derivatives are responsible for ROS generation. In contrast, the aromatic chemical fraction induced an effect also seen with a mixture of PAH. Ambient ultrafine PM induced a combination of polar and aromatic species effects, whereas polystyrene ultrafine particles were inactive in this regard. Furthermore, the aliphatic fraction did not affect ROS production. The PAH component of urban PM has also been implicated in PM-related mutagenicity (Somers et al., 2004), and prenatal exposure to PAH resulted in chromosomal aberrations in umbilical cord blood (Bocsay et al., 2005). These studies suggest that the effects from DEP and some other types of particles are mediated by chemicals that may be adsorbed onto the particulate surface, rather than due to the particle core, and that these adsorbed chemicals likely include OC compounds.

Although many of the individual components of DEP can be toxic, it seems likely that toxicity of DEP, and most likely various other types of PM, may also be due to combined chemistry of the proximal chemical entities contained within the particles. That is, the localization of redox active organic and inorganic agents contained in a carbon core matrix can produce chemically active catalytic particles, whose overall chemical reactivity may be greater than the sum of the individual components (Pan et al., 2004).

**Secondary Inorganic Sulfates and Nitrates**

Schlesinger and Cassee (2003) provided an extensive review of the toxicology of secondary inorganic aerosols, namely, SO42− and nitrate (including acidic species), as it related to epidemiological health outcomes from ambient PM. Any biological responses in the respiratory tract, such as airway hyperreactivity and changes in pulmonary defense parameters, were noted to occur in relation to the acidity of the exposure atmosphere. Thus, the toxicologically significant secondary inorganic particles probably were those having strong acidity, namely, sulfuric acid, ammonium bisulfate and, under some unusual atmospheric conditions, nitric acid. While some of these species have been related to epidemiological health outcomes from ambient PM, Schlesinger and Cassee (2003) concluded that the toxicological evidence did not support a role for secondary inorganic aerosols in adverse health outcomes noted in such epidemiological studies. This was largely because the ambient concentration of secondary particulate SO42− was generally much lower than the exposure concentrations associated with apparent health effects in the controlled studies. However, the physicochemical characteristics of the SO42− used in the laboratory studies may have differed from those to which human populations are actually exposed in ambient air. (Of course, this caveat likely holds for other PM surrogates used in controlled exposure studies as well.)

Other studies also seem to show that SO42− may not be of significant toxicological importance in terms of overall effects from PM exposure. Using CAPs, effects on a biomarker of cellular stress in human bronchial epithelial cells exposed to concentrated fine PM was not correlated with ambient SO42−, in spite of the fact that it constituted 65% of the particulate mass (Maciejczyk & Chen, 2005). Effects were, however, correlated with certain metals, for example, V and Ni from the...
PM-associated with residual oil combustion. Similarly, another study (Huang et al., 2003) indicated that while metals were correlated with the release of cytokines, \( \text{SO}_4^{2-} \) was not so correlated in this regard. On the other hand, Lippmann et al. (2005) reported a statistical association, based on source apportionment analysis, between the secondary sulfate component of fine particulate CAPs from Tuxedo, NY, and transient effects on heart-rate and heart rate variability in a compromised mouse model, but not in normal animals, involved in a subchronic exposure regime. However, both effects seemed to occur after each daily exposure, rather than during exposure, and no explanation either for this temporal lag in effect or for a biological basis for the relationship between \( \text{SO}_4^{2-} \) and effect was provided.

While acidity of secondary sulfates may be a characteristic associated with some adverse PM-related health outcomes in epidemiological studies, it is unlikely that this property alone is responsible for observed health effects (Dreher, 2000). Any interactive effect of a combination of species would not have been shown by studies using pure laboratory-generated particles of \( \text{SO}_4^{2-} \). It should be mentioned that toxicological effects that may be associated with primary metal \( \text{SO}_4^{2-} \) emissions should not be attributed to a generic species, namely, “sulfates,” if secondary \( \text{SO}_4^{2-} \) has negligible health effects (Grahame & Schlesinger, 2005). In such cases, it is likely that the observed response was due to the metal species rather than the sulfate itself.

**Transition Metals and Metal Compounds**

A role for transition metals in producing adverse health effects is based on their potential for oxidative activity and the production of reactive oxygen species. Similar to the quinones, soluble forms of these metals can be involved in a Fenton-type reaction.

Elevated oxidative stress in the lungs and hearts of rats exposed to CAPs (in Boston) and residual oil fly ash (ROFA) was most strongly associated with metal fractions of these particles (Gurgueira et al., 2002). Molinelli et al. (2002) exposed a human airway epithelial cell line to aqueous extracts of PM collected in the Utah Valley. In this study, part of the extract was treated to remove cations, including transition metals. Cells exposed to the untreated extract showed a concentration-dependent increase in the inflammatory mediator interleukin (IL)-8 compared to controls; cells incubated with the treated extract showed no such change. This suggests that the removal of metal cations attenuated cellular response to the aqueous extract, and supports a role for transition metal involvement in PM toxicity. In this regard, cultured human T cells exposed to 1-\( \mu \)m carbon particles or particles containing both carbon and iron showed increased production of reactive oxygen species with the latter, but not with the former (Long et al., 2005). Finally, Sorensen et al. (2005) found a relationship between the V and Cr components of fine particulate CAPs and oxidative damage to DNA.

It is unclear whether all PM-associated transition metals are equally toxic, or whether there can be a ranking of toxicity related to specific metal content or metal valence state. Furthermore, relative water solubility may also be a factor in modulating biological response. Using aqueous extracts of filter collected PM\(_{10}\) obtained from Utah Valley before, during, and after closure of a local steel mill, Frampton et al. (1999) avoided the issue of water solubility versus insolubility as modulating factors in examining effects of these extracts on human respiratory epithelial cells in vitro in terms of oxidant capacity, cytotoxicity, and induction of proinflammatory cytokine expression. The extract with the lowest metal content, specifically soluble Fe, Cu, and Zn, showed no cytotoxicity, minimal induction of cytokines, and lowest oxidant generation ability compared to extracts from PM having higher metal content. However, when metals were removed from the extract prior to exposure, there was still an effect of these extracts on at least one endpoint, namely, phagocytic activity of macrophages. Thus, the soluble metals were probably not the only components responsible for observed effects.

There is additional evidence for toxicity of soluble metals that may relate to PM exposure health outcomes. When ambient PM from St. Louis, MO, Washington, DC, Dusseldorf, Germany, and Ottawa, Canada, were tested for toxicity, the observed greater response to Ottawa PM was postulated to be due to its higher content of water soluble metals (Costa & Dreher, 1997). Other studies have indicated that Zn in PM may be responsible for various pulmonary effects, such as inflammation, necrosis, and airway hyperreactivity (Adamson et al., 2000; Dye et al., 2001; Kodavanti et al., 2002a; Gavett et al., 1997). Human bronchial epithelial cells exposed to extracts of PM collected in Taiwan showed a correlation between cytokine production and metal content, with effects on some cytokines correlating with Cr and Mn, and others with Fe and Cr (Huang et al., 2003). In a study using ROFA, particles with higher Zn content resulted in greater pulmonary inflammation and airway responsiveness than did particles with higher Ni or V content (Gavett et al., 1997). In a similar study, human bronchial epithelial cells were exposed to concentrated fine fraction PM (Maciejczyk & Chen, 2005). The greatest correlation to the biomarker of response, namely, nuclear factor kappa B (NF-\( \kappa \)B), an indicator of cellular stress, was seen with residual oil sources, using Ni and V as markers. Mice with allergic airway disease were found to have increased proinflammatory cytokines following exposure to PM\(_{2.5}\) recovered from ambient air filters from different areas, but only PM having higher metal content (specifically Zn, Mg, Pb, Cu, Cd, and As) resulted in increased airway responsiveness (Gavett et al., 2003). While the apparent differences in response to various metals may seem to add to inconsistencies between toxicological studies, they do, in fact, support the idea that the endpoint examined is critical in reaching any conclusion as to the efficacy of specific metals and/or that effects may be linked to specific valence state.

**Crustal-Associated Chemicals**

Early studies often used ash from the Mt. St. Helen’s volcanic eruption as a surrogate for crustal material. The advantage to using this material is its isolation of the inorganic metal
oxides from humic and other organic material associated with soil dust normally found in ambient PM. The studies using volcanic ash tended to show that such particles were relatively inert and generally noninflammatory (U.S. EPA, 1996).

Some more recent studies have examined effects of other components generally associated with crustal PM. Using fine particulate mode CAPs from the Boston area, Clarke et al. (2000) noted that Al and Si were correlated with increased pulmonary neutrophils in lung lavage samples and increased total peripheral blood white cell counts in dogs. However, since crustal PM does not occur as a large fraction of material in the fine particulate mode, the investigators hypothesized that the findings indicated that the Al–Si factor was a surrogate for other particles. In a subchronic exposure study to fine particulate CAPs, Lippmann et al. (2005) reported a statistical association, based on source apportionment analysis, between the respired soil factor and transient effects on heart-rate and heart rate variability in a compromised mouse model, but not in normal animals.

Batalha et al. (2002) showed that exposure to concentrated ambient PM$_{2.5}$ from Boston resulted in small pulmonary artery constriction in rats that was associated with PM mass, Si, Pb, sulfate, EC, and OC, but with Si showing the strongest association. Again, it is not clear if the effect was actually due to the Si, or whether the Si was a surrogate for another component of PM. Wellinghaus et al. (2003) noted that exposure of dogs (having coronary occlusion) to concentrated PM$_{2.5}$ from Boston resulted in elevation of the ST segment on the electrocardiogram (ECG), an effect that was not well correlated with total PM mass or number but was related to Si mass concentration. As another example, Kobzik et al. (2001) noted that the degree of bronchoconstriction in mice was associated with an Al–Si factor. As already described, this may not necessarily mean that Si per se is toxic, but that components of ambient PM, whose concentrations vary with that of Si, may be toxic; Si concentrations generally are highly correlated with other crustal elements, such as Al and Ca. Finally, Veranth et al. (2004) observed that some representative western U.S. soil dusts in the fine mode could induce proinflammatory cytokine signaling in vitro, but that other crustal-related PM, namely kaolin clay and aluminum oxide, was benign in this regard.

**Biogenically Derived PM**

PM may contain OC components of biological origin. This can include pollens, molds, spores, and biological toxins, such as bacterial endotoxin. In addition, a major fraction of biogenically derived OC comes from atmospheric reactions of volatile organic compounds (VOC), such as terpenes. Products of biogenic vapor oxidation in the atmosphere include highly oxygenated species, ring compounds, and probably organo-nitrates and amines. The potential health effects of exposure to these biogenically derived chemicals are largely unknown.

While exposure to biological particles in occupational settings has long been known to be associated with various respiratory tract illnesses (Brooks, 1998; Kline & Schwartz, 1998), the health significance of biogenically derived components of ambient PM has not received as extensive study as the other chemical constituents already discussed. Ambient PM of biological origin can have a broad size range, from ultrafine to coarse, thus crossing all size modes of interest for regulatory purposes. However, endotoxin levels are generally higher in coarse mode PM than in smaller size modes, and the former may be more potent than the latter in inducing pulmonary inflammation if endotoxin is present. Similarly, microbes preferentially found in the coarse fraction of ambient PM may be involved with inflammation induced by these particles (Becker et al., 2002).

In vitro studies have shown that coarse-mode particles may be effective in inducing toxicity, and some have indicated that the coarse mode was more potent than either the fine or ultrafine modes and that relative potency depended on the season during which tested particles were collected (Dailey, 2002; Shi, 2003); seasonality that would likely affect biogenic and/or chemical constituents. Li et al. (2002b) noted that induction of oxidative stress was correlated with a higher PAH content of coarse PM during the fall and winter months, while such association with the coarse mode was not observed at other times of the year when fine mode PM had higher levels of PAH.

Some PM may act as adjuvants; that is, specific PM components may enhance the antigenicity of other inhaled materials, including other types of PM. For example, it has been suggested that DEP may have adjuvant activity with some antigens (Muranaka et al., 1986; Takafuji et al., 1989). DEP has also been shown to increase the production of immunoglobulin (Ig) E in nonatopic individuals (Diaz-Sanchez, 1997). When both fine and coarse PM collected from various sites in Europe were tested for adjuvant activity in an allergic mouse model, both size fractions showed various degrees of such activity in combination with allergens (Steerenberg et al., 2005). While adjuvant activity may be associated with adsorption of allergens onto PM, such activity may also result from exposure that results in increased tissue sensitivity to subsequent exposure to other allergens (Nel et al., 1998). Thus, biologically derived PM may interact with other types of PM in producing adverse health outcomes.

**Epidemiological Inferences for Health Effects**

As observational sciences, environmental epidemiology and allied disciplines face numerous challenges in addressing the question of what PM constituents contribute to observed associations between health outcomes and exposure. In some respects, the limitations of epidemiology mirror those faced by toxicology. While the latter can precisely control for exposures, epidemiology almost always assesses pollutants that accompany PM and that also may vary in concentration and that often, to unknown degrees, may contribute to the relevant PM exposure of study subjects. While toxicology suffers from the criticism that laboratory exposures fail to represent adequately the real ambient exposure experience, epidemiological studies can be criticized for assessing real exposures based on existing
metrics, but not contributing to understanding the underlying PM constituents or other components of the ambient air pollution mix that may harm human health.

The assessment of constituent- or source-specific effects in epidemiology studies relies on a comparison of associations observed with different markers of exposure. Such comparisons are possible only across constituents with identical, or at least similar, validity to characterize “exposure.” The fundamental assumption is that the “exposure term” used in the models reflects comparable personal exposure on the relevant time and population scale. Exposure studies contribute new insights to understanding the link between personal, indoor, outdoor, and fixed site monitor data (Meng et al., 2005; Kim et al., 2004; Brunekreef et al., 2005; Oglesby et al., 2000; Janssen et al., 2000). Given that the majority of epidemiological studies did not include personal exposure measurements, but usually relied on ambient monitoring data, understanding the link between the measured marker of pollution and “personal exposure” to the health relevant constituent(s) is crucial to appropriately interpret findings and to comprehend the limitations of constituent or source comparisons.

To compare effects across source-specific markers, one has to reassure that the validity and accuracy of the surrogate measure to reflect “personal exposure” is sufficiently equal across the markers. The Individual Exposure Model (IEM) (Wu et al., 2005) illustrates the difficulties of reflecting personal or individual exposure equally across surrogate markers. The IEM relies on integrated exposures from microenvironments [m = 1 . . . M (residential outdoor, residential indoor, school or work outdoor, school or work indoor, and in vehicle)] where subjects spend most of their time, to compute the time-weighted average exposure (TXi) for a specific individual, i, as follows:

\[ TX_i = \frac{1}{T} \sum_{m} X_{im} \Delta t_{im} / \sum_{m} \Delta t_{im} \]

where \( X_i \) is the cumulative exposure to individual \( i \); \( X_{im} \) is the pollutant concentration in subject \( i \)'s microenvironment, \( m \), and \( \Delta t_{im} \) is the time spent by individual \( i \) in microenvironment \( m \). These quantifiers are summed for all microenvironments. As a general rule, the higher the spatial variability of a constituent or source-specific pollutant, the less likely it is that a point measurement, such as a fixed-site monitor, reflects personal exposure of the population at large. Indoor environments are the prevailing spaces where people spend over 90% of their time (Leech et al., 2002). Moreover, certain activities, such as commuting, may lead to disproportionately high exposures to some pollutants (Fruin et al., 2004). Thus, the criterion to judge validity of the assessment is, in essence, the spatiotemporal variability, defined as the difference in exposure to ambient pollutants indoors or during commute as compared to the levels at the location used for exposure assignment.

Overall, the existing studies confirm that the “personal exposure validity” criterion of any marker of exposure that has not been measured on people may depend on the employed study design. Given a specific study design, the “exposure validity” criterion may grossly vary across the different constituents used as markers of exposure. Any comparison of source-specific or constituent-specific effects of ambient pollution is limited if no personal exposure measurements, proxies such as household measurements, or other cross-validation information are available through biomarkers, blood lead being an example. It is essential, then, to examine results from a wide range of study designs, each with specific strengths and limitations, for addressing this exposure validity criterion.

The use of pollutant markers is key in epidemiological studies. Linking certain chemical components with known sources that may dominate the presence of that component in ambient air has often been attempted. Urban trace gas constituents, for example, that are associated with major sources include: carbon monoxide (CO), mainly with motor vehicle emissions, but incomplete combustion in general; nitrogen oxides (NOx), associated mainly with motor vehicles, but also affected by stationary source emissions, including power plants, and in some areas by seaports and airports; and sulfur dioxide (SO2) associated with fossil fuel combustion, often dominated by coal- or oil-fired power plants but with industrial point sources and diesel and bunker fuel as additional sources. PM components linked to sources include: SO2^2-, generally a minor primary effluent but often a major secondary atmospheric oxidation product of SO2 associated with sulfur containing fossil fuel combustion; carbon (EC and OC) originating from incomplete combustion or secondary chemical reactions; and metal oxides or salts. Certain specific chemicals within PM can sometimes also be traced to specific sources, such as Pb (to automobile exhaust prior to 1985), Se (to coal combustion), and V or Ni (to residual oil combustion). These markers have been used in some recent studies to infer, although indirectly, the presence of source contributions in health-related PM associations.

Source identification approaches, discussed later, have important limitations, including the potential for identifying different sources affecting the same observational data. In addition, the interpretation of factor analysis results has a subjectivity that needs to be accounted for by careful evaluation of the results in the light of available source profiles to insure that all the contributing and location specific issues are addressed.

**Health Effects of PM Revealed Through Different Study Designs**

Epidemiological studies include six different classes of design that may contribute to causal inferences: time-series studies relying on short-term temporal exposure contrasts; panel studies conducted on small populations and involving acute exposures; cross-sectional studies focused on prevalent health conditions; case-control studies that examine chronic or longer-term exposures through spatial exposure contrasts; cohort studies of chronic exposures that track health over time but usually rely on temporally limited spatial exposure contrasts; and “intervention studies” that rely on regulatory or other natural changes that alter...
ambient concentrations, which, in turn, may lead to changes in health. Intervention studies arguably offer the best opportunity for discerning specific effects, although they must be viewed in the context of evidence from other study designs because the specificity of the intervention often limits generalization of the results. All of these designs have yielded information about the association of health effects with PM and, indirectly, with the pollutant mix of both PM and gases.

The following sections provide an evaluation of studies in the classes just noted, with a focus on studies that may contribute to the assessment of PM constituent- or source-specific health effects. In conducting this review, the “mind map” illustrated in Figure 1 was followed. This figure graphically depicts the numerous issues that may influence an epidemiological study of PM health effects. While this map was not rigidly adhered to for all analyses herein, the attempt was made to assess specific sources, PM constituents, copollutants, pollutant/source factors, other exposure markers, type of exposure contrast, inclusion of different health outcomes, and susceptible subgroups investigated. The intent is not to replicate available reviews (WHO, 2000; U.S. EPA, 2004; NRC, 2004) but, rather, to select studies that have had a major impact on the field to illustrate how the different study designs help to inform the above issues. All reviewed health effects studies are summarized in Table 2, which draws from the mind map, thus emphasizing achievements, gaps and needs in an overall attempt to identify the harmful constituents or properties of PM and their sources. Of the various methods and studies reviewed, few specifically targeted sources and constituents, but the proximity, factor analysis, and intervention studies may offer the most promise for understanding the relative health effects resulting from different types of PM.

**Multicity and Multipollutant Time-Series Models**

Time-series studies seek to assess relationships between daily or multiday ambient pollution concentrations and subsequent mortality occurring within one or a few days. Although these studies have uncovered significant associations between
### TABLE 2
Comparative evaluation of cited epidemiological studies

<table>
<thead>
<tr>
<th>Study design</th>
<th>Exposure contrast</th>
<th>Sources</th>
<th>PM size fraction</th>
<th>PM-constituents</th>
<th>Co-pollutants</th>
<th>Other exposures</th>
<th>Temporal</th>
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<th>Study population, susceptible subgroups</th>
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Note: Symbols: * Reanalysis available in HEI 2003 special report; %, case cross-over study; f, source specific factors derived from factor analysis; CS, factor for crustal material, soil, resuspended particles, derived from factor analysis; INC, incinerator; HS, hot spots; CH, coefficient of haze; E, Elemental analysis of PM, H+, acidity of PM, HAP, hazardous air pollutant as defined by U.S. EPA; Bz, benzene; TRS, total reduced sulfur; TC, traffic counts; 7Ad, 7th day Adventists; C, children; E, elderly; m, males.
elevated mortality and acute exposure to PM (Samet et al., 2000b; Burnett et al., 1998), a recently discovered programming error has called into question the results from these analyses (Ramsay et al., 2003; Knight, 2002), resulting in concern about the magnitude and validity of the association (Revkin, 2002). Due to the statistical problem, this review focuses on those studies published after 2002 using appropriate methods, or on those reanalyzed and published as revisions to the original findings. It is worth noting that a major reanalysis sponsored by the Health Effects Institute (HEI) reported that the majority of conclusions drawn from earlier time-series studies remained unchanged but, in some instances, estimates were reduced by application of corrected statistical methods (HEI, 2003). Focus is also on those studies that use factor analysis or other source apportionment techniques to identify likely sources of ambient PM and any health associations.

Large multicity studies, such as Air Pollution and Health: A European Approach (APHEA)(Katsouyanni et al., 2001; reanalyzed in HEI, 2003), the National Mortality and Morbidity Air Pollution Study (NMMAPS) (Samet et al., 2000a), and the Canadian multicity time series (Burnett et al., 2000; reanalyzed in HEI, 2003), cover many geographical regions across which composition of PM differs, or across which markers such as SO$_4^{2-}$ may actually represent mixtures of PM pollutants from different sources. For example, across the United States, a gradient of increasing SO$_4^{2-}$ and carbon levels is apparent from west to east (NARSTO, 2004; Hidy & Blanchard, 2005). There also are gradients for the proportion of particles in PM identified with the earth’s crust (north–south in addition to east–west), and the proportion of SO$_4^{2-}$ attributed to coal-fired power plants, compared to that from other fossil fuels, residual oil burning, or metal SO$_4^{2-}$, among total SO$_4^{2-}$.

The U.S. NMMAPS study computed PM$_{10}$ effects by region. Significantly, elevated risks were detected in the Midwest, Northeast, and in Southern California. As discussed in a subsequent commentary, no source-specific conclusions could be drawn because the NMMAPS study provided only a superficial analysis of issues that may have resulted in the heterogeneity. Thus, drawing source- or constituent-specific conclusions remains difficult even with this extensive multiregion analysis. Throughout the original NMMAPS analysis, PM$_{10}$ mass concentration was the only PM marker used, and this was the only pollutant that remained significant in multipollutant models. More recent updates have also found significant, but relatively smaller, effects for O$_3$ (Bell et al., 2004).

Zeka and Schwartz (2004) reanalyzed the NMMAPS data using a new technique designed to account for exposure measurement error. Their results indicate a slightly larger effect for PM$_{10}$ than found earlier, but also a significant effect for CO. This finding led the authors to conclude that CO or particles from motor vehicles were potentially more significant threats to public health than previously reported in the original study by Samet et al. (2000b). Roemer and van Wijnen (2001) also observed stronger time-series associations for mortality with ambient PM for those living along busy roads. This finding cannot be solely interpreted as an effect of traffic sources, but may be due to higher susceptibility of people living very close to heavily trafficked areas, or to interactions between pollutants. Canadian studies by Burnett and colleagues (2005) have reported significant associations with NO$_2$ that were independent of PM. This, again, indirectly implicates traffic sources as a potential source of acute health effects. Similar conclusions were drawn in earlier studies by APHEA investigators, who found consistently larger PM$_{10}$ effects in cities with higher NO$_2$ (Samoli et al., 2005).

The APHEA study also reported higher PM effects in areas with lower standardized mortality rates, and this is a good example of the complexities involved in attributing the elevated health effects to PM from traffic related sources. In areas with lower baseline mortality, detecting relatively small signals from air pollution may be easier due to the lack of competing causes. Areas with lower mortality corresponded to areas with higher NO$_2$, suggesting that disentangling the source specificity from other population health characteristics may prove difficult with this study design.

In a study of cardiovascular disease (CVD) visits to emergency rooms in Atlanta, GA, Metzger et al. (2004) examined numerous physiochemical components of PM and other urban air pollutants. They reported positive significant associations between CVD visits and ambient concentrations of CO, NO$_2$, PM$_{2.5}$, OC, EC, and oxygenated hydrocarbons. Copollutant and multipollutant models generally showed attenuated effects, often indistinguishable from unity. In many instances, however, the larger positive effects that remained in the multipollutant models were indicative of traffic pollution, especially CO. The authors suggested that single and multipollutant results point toward a traffic effect on CVD-related emissions, with the strongest effect appearing on the day of hospital admission.

### Source Apportionment in Time Series Models

Various approaches have been developed to apportion pollutants to specific sources and, thus, to try to relate specific PM constituents to health outcomes. At this point in time, these approaches have generally been restricted to source apportionment of measurements taken at fixed-site monitors, with application to source factor/time-series analyses, and have not used monitoring data acquired prior to 1999, as the U.S. EPA (post-1999) speciation network database only recently has become available.

Source apportionment methods involve the application of a chemical mass balance (CMB) or various forms of factor analysis. CMB makes use of chemical tracers, or measured source profiles for major source categories, to quantify PM source contributions. Factor analysis separates the variance in chemical composition into statistically independent factors that are identified with PM sources on the basis of source profiles, or other subjective and objective information about source chemistry.

The earliest time-series study of this kind focused on PM$_{10}$ in the Boston area (Thurston & Spengler, 1985). More recently, this has been extended to the Harvard Six Cities (U.S. eastern)
data to identify source categories and health effects (Laden et al., 2000; HEI, 2003), and to air pollution in Phoenix, AZ (Mar et al., 2000; HEI, 2003).

The Laden et al. (2000) “meta-analysis” has yielded a classification of major fine particle sources according to their apparent impact on health effects in Boston, Steubenville, OH, Portage, WI, Knoxville, TN, St. Louis, MO, and Kansas City, KS. When combining the data from all six cities, the results suggest that mortality levels in the 1980s in these cities were most strongly impacted by light duty motor vehicle emissions (using Pb as a tracer for 1980s gasoline), followed by coal combustion emissions (using Se as a marker for coal ash). Separately, an association was found with a sulfur factor (S; sulfur or SO$_2$ tracer for 1980s gasoline), impacted by light duty motor vehicle emissions (using Pb as a surrogate for motor vehicle emissions (e.g., CO and NO$_2$) and weaker associations with an SO$_2$ factor, PM$_{2.5}$, or PM$_{10-2.5}$. Specifically, cardiovascular mortality also was associated with these pollutants, along with PM$_{10}$ and EC concentrations. Differentiation by factor analysis to identify source signatures indicated a negative association with vehicle emissions and local SO$_2$ levels. No significant association with mortality and soil dust was found. An association with an SO$_2$ factor was determined for total mortality without a time lag, but a negative association was noted using a 3-d time lag. Unlike two of the other factor analyses for Phoenix PM sources, the Mar et al. analysis did not distinguish SO$_2$ from regional power production and smelter operations. This leaves an ambiguity in the SO$_2$ source assignment.

### Panel Studies

Panel studies focus, by default, on acute effects of ambient air pollution. A number of repeated measurements among panel members are compared with the ambient conditions on that day or a few days prior. Participants serve as their own control; thus, only time-varying factors can potentially confound results. Panel studies assume that the pollution terms used in the model reflect personal exposure of each subject on a specific day. Given that spatial variation differs across pollutants and properties and that time–activity data are usually not integrated, the use of fixed-site monitoring data is inappropriate for comparing the health effects of various PM constituents.

To distinguish effects of different pollutants and constituents, panel studies ultimately need personal exposure assessment. Two panel studies employed personal exposure assessment methods; others relied on fixed-site data. The first, a study among elderly in Baltimore, provides evidence that heart-rate variability is affected by combustion-related pollution, indicated with ambient PM$_{2.5}$ mass concentration. However, results were very sensitive to 2 rainy days where PM were thought to be transported from rural Pennsylvania, whereas pollution on the other 22 days originated mostly from the Midwest and Northeast (Creson et al., 2001). The study measured pollutants in a retirement center and thus reflects to a high degree personal exposure of subjects having limited mobility. However, source apportionment of the air mixture cannot be derived from this study. The specific contribution of traffic, industry, power plants, or other stationary sources to the more toxic air parcels cannot be determined.

A Vancouver-based study of 16 elderly patients with chronic obstructive pulmonary disease (COPD) provides the most
extensive personal exposure measurement and estimation approach done in panel studies (Ebelt et al., 2005). The study suggests that personal exposure to pollution from outdoor origin, rather than total personal PM mass exposure, exerts the largest health effects. The estimates for changes in pulmonary function were smaller (and nonsignificant) for personal sulfate exposure as compared to estimated nonsulfate PM from outdoor origin. For other outcomes, such as autonomic function of the heart, this distinct pattern was less clear. As also noted by the authors, SO$_4^{2-}$ levels were low in Vancouver ($2 \mu g/m^3$ on average), and measurement error may have been larger for the SO$_4^{2-}$ component. It is difficult to further interpret the observed pattern from a more specific source perspective. The nonconclusive findings based on SO$_4^{2-}$ as the marker of personal exposure cannot be generalized to all of North America because SO$_4^{2-}$ in the Northwest and in the East potentially has different sources, and it occurs at higher concentrations in the East. Although Creason et al. and Ebelt et al. reported similar findings, the differences in sources and pollution levels make the studies incomparable. The studies do, however, serve to emphasize the notion that source-specific relevance of PM differs across various health outcomes.

Other panel studies used data available from only one monitoring site, and no personal exposure monitoring. They demonstrate the difficulty of interpreting findings for specific sources or constituents in panel designs. The asthma panel from Yu et al. (2000) implies that combustion-related ambient air pollution, indicated with CO and PM, leads to asthma symptoms. Their null or unclear findings for SO$_2$ may be the result of limitations in the exposure assignment. As shown by Ito et al. (2004), spatial correlations between monitoring locations are extremely poor for SO$_2$ concentrations in the Northwest. As a result, the single-monitor estimates of SO$_2$ concentration may be weakly associated with the subjects’ personal exposures to SO$_2$.

The Eastern U.S. asthma panel of Gent et al. (2003) also confirms associations between combustion-related pollution and symptoms among asthmatics, but precludes pollutant-specific conclusions. They report consistent associations for ambient O$_3$ but not for ambient PM, both measured at a few fixed sites. Sarnat et al. (2001, 2005) have shown for the Baltimore area that ambient O$_3$ concentrations are well correlated with personal PM exposure, but very poorly associated with personal O$_3$ exposure. Thus, ambient O$_3$ may be a marker for personal exposure to PM. It is not possible to interpret these findings for specific sources, such as power plants, motor vehicles, or industry, as these all may contribute to ambient PM and O$_3$.

The PEACE study was a European multicenter panel with conflicting nonconclusive main results on respiratory health (Roemer et al., 1998). A further analysis provided estimates not only for PM$_{10}$ mass but also for metal content of PM$_{10}$, all measured at a fixed site (Roemer et al., 2000). As shown in a recent report (HEI, 2003), spatial variability and thus the association between fixed sites and personal concentrations dramatically differ across constituents of PM$_{10}$. Fixed-site sulfur on PM was highly correlated with personal S exposure, whereas for metals, correlations were much lower (Brunekreef et al., 2005; Ito et al., 2004). Therefore, the lack of association between the onset of symptoms and, for example, metals may be due to poor exposure assignment (Roemer et al., 2000). It is not possible to use this study to differentiate the health relevance of various PM constituents.

**Cross-Sectional Studies**

This type of study seeks to assess associations between disease status, or a chronic functional condition, and pollution exposure at one point in time, while controlling statistically for potential confounding variables. As such, the main exposure contrast is spatial between individuals or areal units. For example, European research findings suggest that if traffic is indeed an index for PM, higher traffic counts or emissions near the residence may exacerbate asthma and related respiratory symptoms (van Vliet et al., 1997; Ciccone et al., 1998; Venn et al., 2000, 2001).

Venn et al. (2001) characterized exposure to traffic by distance to a main road. Among those living up to 150 m from roads, distance was strongly associated with wheezing in primary school girls, and in both girls and boys from secondary schools. The association was mostly driven by the risk gradients within the first 90 m, with risk falling to baseline concentrations at > 100 m. This study underlines the need to focus the “proximity domain” on the first 0–100 m. In fact, a previous evaluation of the same group failed to observe significant effects in an analysis that was not sensitive to the short distance proximity buffer (Venn et al., 2000).

A German study by Nicolai et al. (2003) found similar results. For children living within 50 m of the road, traffic counts were significantly associated with cough, current asthma, and wheeze. The results suggest a dose-response relationship, with higher traffic counts associated with more severe symptoms. They reported a weakening in the traffic-adverse health associations if the buffer was widened from 50 m to 100 m and 300 m.

An earlier study by van Vliet et al. (1997) determined both distance from freeways and density on these freeways. Among children living within 1 km of freeways, those living within the first 100 m had higher prevalence of chronic cough, wheezing, and doctor-diagnosed asthma, but associations were statistically significant only among girls. The relatively small distance effects again implicate traffic emissions and, potentially, their PM constituents as the source of observed health effects.

Similarly, in North America, cross-sectional evaluations of prevalent asthma and symptom severity have also demonstrated associations with markers of traffic or proximity to roadways (McConnell et al., 2003). Jerrett et al. (2005a) reported elevated risks of asthma in adults aged 20–44 yr, with a distinct decay of the effect size with increasing distance to major roads. These results were robust enough to control for occupational exposures and exposures to industrial-source SO$_2$ for women, but not for men. An analysis of the Children’s Health Study (CHS) among a subsample with home-based exposure measurements revealed
an association between asthma prevalence and home and outdoor NO₂, as well as other markers of local traffic (Gauderman et al., 2005). The Gauderman et al. study (2005) used NO₂ measured at approximately 250 homes to assess the relationship between this marker for traffic pollution and asthma in a subset of the CHS. Reported effects were significant and large (relative risk, RR, was ~1.80 over the interquartile range of exposure). It should be noted that many traffic-related studies using proximity only estimate indirectly a link with PM, as traffic-related gaseous emissions may be used as possible surrogates for PM or may themselves be associated with health outcomes. Thus here, as well as in other discussions, these issues need to be kept in mind.

A few earlier studies investigated proximity to point sources, including coking operations and hazardous waste incinerators. For the most part, proximity to incinerators did not result in elevated rates of oral, pharyngeal, and lung cancers (Elliott et al., 1992), but subsequent substudies did report elevated cancer rates near one site, implicating putative air emissions as the likely source (Diggle et al., 1999). The extent of study for putative sources appears much smaller than for the traffic studies, perhaps due to the complexity of studying point sources that may depress rents and attract susceptible individuals into the proximity, known generally as an environmental justice or equity effect (Been, 1987, 1993), and due to the potential long-range transport from tail smoke stacks, leading to only small spatial exposure contrasts. In addition, subjects working in point source facilities may live close by; thus, effects of occupational exposure cannot easily be distinguished from those due to ambient exposure. This makes assessment in local areas more difficult due to dispersion from the source to areas farther away.

Reynolds et al. (2003) used modeled point-source hazardous air pollutant estimates at the census tract level to investigate associations with childhood leukemia in California. This method may have significant exposure measurement error due to the combination of inaccurate geo-codes for industrial facilities and the modeling process for prediction. In spite of this potential for error, they still reported significantly elevated risks for people residing around point sources, such as industrial facilities, many of which would emit hazardous PM.

A recent study from the United Kingdom showed similar results (Knox, 2005). It examined fatal childhood cancers over a 14-yr period across the United Kingdom in relation to toxic hotspots, including PM₁₀ emitters, identified through a government atmospheric emissions inventory. Proximity of birth to hotspots related significantly to these cancers, and many contaminants, including PM₁₀, showed significant associations in this regard. Of the various contaminants, the author concluded that the most significant risks appear related to some form of hazardous waste incineration or oil burning or evaporation, suggesting that putative emissions from industrial sources inhaled by the mother may cross the placenta to affect the fetus.

One of the more novel cross-sectional studies from a mechanistic perspective was one associating carotid intima media thickness (CIMT), a preclinical measure of atherosclerosis, with ambient particles in the Los Angeles metropolitan area (Kunzl et al., 2005). This is consistent with the observed effects of PM₂.₅ on atherosclerosis in hyperlipidemic rabbits (Goto et al., 2004; Suwa et al., 2002). The systemic response to ambient PM may amplify and expand the oxidation of low-density lipoprotein (LDL) cholesterol among susceptible subjects, consequently contributing to injury of the artery wall (Goto et al., 2004; Ross, 1999). While useful for opening new avenues to link toxicology and epidemiology, the results shed light on the complexities of disentangling underlying susceptibilities from particle constituents or size modes. In the case of Los Angeles, though, the majority of PM₂.₅ mass derives from nitrate and OC originating principally from transportation sources, again implicating mobile sources as an underlying major contributor to health effects.

**Case-Control Studies**

Case-control studies seek to identify cases with the health outcome of interest and match these to controls, who share similar individual characteristics (e.g., age and gender), but who are unaffected by the health outcome of interest. Under the null hypothesis, cases and controls should have a similar exposure distribution. Most case-control studies published to date focused on characterization of exposure to traffic-related pollutants.

Case-control studies on asthma and residential exposure to traffic suggest that traffic density 300 m from a child’s house may affect asthma status (Zmirou et al., 2004), or hospital or medical care visits among asthmatics (Lin et al., 2002; English et al., 1999). Lin et al. (2002) studied children aged 0–14 yr admitted to the hospital in Erie County, NY. The children hospitalized for asthma were more likely to be exposed to high traffic density within 200 m of their home. Effects were not observed with distance to state roads, or to traffic outside of the 200 m radius.

Negative findings have also appeared in some case-control studies of asthma, raising questions about consistency in effects. Earlier studies from England report no significant effects on asthma from traffic within proximity to major roads (Livingstone et al., 1996). A case-control study nested in the Oslo, Norway, Birth Cohort used NO₂ sampling, home indoors, home outdoors and on person, as well as distance to street (Magnus et al., 1998). Episodes of bronchial obstruction up to age 2 yr were not associated with distance to street (based on four categories), with three categories made in the 0–100 m buffer and one on greater distances. Risks tended to decrease with proximity, but were not statistically significant. Distance to "a main road" was based on a questionnaire, which may be an unreliable indicator of true exposure. Moreover, “asthma” is ill-defined in early life, and self-selection of residential location among families with asthma was not controlled. Beyond the general inference that some element of motor vehicle emissions appears related to respiratory health outcomes in some places, these studies cannot be used to make any definitive conclusions about PM or other constituents of the complex mix of pollutants.
near roadways, and need to be put into the context of traffic-related findings in other study designs (see cohort studies).

Lung cancer is another important health outcome that has been investigated through a case-control design. Barbone et al. (1995) and Nyberg et al. (2000) both used case control designs to test associations between exposure to pollution and lung cancer. Barbone et al. compared polluted city center areas to suburban residences, and found significant risks for small and large cell carcinoma of the lung. Although useful in establishing an association, the Barbone et al. study does little to illuminate the type of pollutant responsible for the association, as industrial and heating source PM may also be higher in central city areas of Europe. Nyberg et al. used extensive traffic, land use, and monitoring information to reconstruct long-term exposure to NO\textsubscript{2} and SO\textsubscript{2} over a 30-yr period. They reported increased risks for lung cancer in relation to NO\textsubscript{2}, but not to SO\textsubscript{2}; however, concentration ranges were broader for NO\textsubscript{2} (more than threefold) than for SO\textsubscript{2} (twofold). The period of exposure approximately 20 yr before the event was found to associate most strongly and significantly with lung cancer, adding to the biologic plausibility of their findings, given the long latency for cancer. Neither study directly assessed PM concentration or constituents, but the gases examined can be surrogates for copollutant emissions of PM. While a quantitative difference related to PM does not necessarily follow from these studies, the results are at least suggestive for a relevant PM contribution from traffic sources.

Ambient air pollution may contain numerous carcinogens (Cohen, 2003). Thus, null or inconclusive findings must be put in the context of the methodological challenges to assess associations. The long latency for this disease increases the potential for violation of the exposure equality criterion between subjects and precludes specific reference to sources or constituents. Personal mobility may also confound associations, given the latency for disease onset (Knox, 2005). These methodological challenges effectively mean that the same exposure term may have different implications depending on the changes in residential location and daily personal monitoring.

Cohort Studies of Mortality

Cohort studies seek to enroll samples of the population living in a range of air quality at one point and then follow all subjects over time to assess whether air pollution exposure associates with the onset of disease or death. Although cohort studies are often considered the “gold standard” for assessing health effects from air pollution (Kunzli & Tager, 2000), only six distinct cohort studies have been examined with respect to impacts of long-term air pollution exposure and mortality: the Harvard Six City cohort (Dockery et al., 1993), the American Cancer Society (ACS) cohort (Pope et al., 1995, 2002; Krewski et al., 2000; Pope et al., 2002; Jerrett et al., 2003, 2005b), the Adventist Health Study cohort (Abbey et al., 1999), the Netherlands Diet and Cancer cohort (Hoek et al., 2002), the Canadian Firestone clinic study (Finkelstein et al., 2003, 2004), and the Norwegian health study (Nafstad et al., 2004). Collectively, these studies demonstrate a significant, positive association between mortality and chronic exposure to PM, especially PM\textsubscript{2.5}. These studies have also found significant associations between mortality and O\textsubscript{3} (Abbey et al., 1999), NO\textsubscript{2} (Nafstad et al., 2004), SO\textsubscript{2} (Krewski et al., 2000; Pope et al., 2002), and traffic buffers (Finkelstein et al., 2004; Hoek et al., 2002).

Two large national-level U.S. studies based on the American Cancer Society Cohort (Pope et al., 2002; Krewski et al., 2000) tested relationships between TSP, SO\textsubscript{4}\textsuperscript{2-}, PM\textsubscript{10} or PM\textsubscript{2.5}, and mortality. A suite of copollutants of potential interest, including O\textsubscript{3}, NO\textsubscript{2}, CO, and SO\textsubscript{2}, was also tested. The studies reported associations between mortality and PM\textsubscript{2.5} and SO\textsubscript{4}\textsuperscript{2-} that were robust to control for occupational exposure, individual smoking and other covariates, and remained significant in multi-pollutant models. In line with other studies, TSP and PM\textsubscript{10} had smaller and less significant effects.

In the ACS study, SO\textsubscript{2} exerted independent significant effects and confounding influence on the associations between SO\textsubscript{4}\textsuperscript{2-} and mortality. In the Krewski study, SO\textsubscript{4}\textsuperscript{2-} effects were reduced by as much as 50% and were rendered insignificant when SO\textsubscript{2} was inserted in the model as a copollutant. The extent of confounding was sensitive to whether spatial regression methods were used to control for residual spatial autocorrelation, with the confounding effect being most severe in models controlling for such autocorrelation.

Although the confounding of SO\textsubscript{4}\textsuperscript{2-} effects may have resulted from incomplete filtering of autocorrelation in the SO\textsubscript{2} due to a small-area spatial variability compared to sulfates, it also may have indicated that SO\textsubscript{2} acted as a surrogate for point source emissions from combustion sources. This latter explanation is augmented by a finding of significant effect modification by education status, such that those with less than high school graduation had larger effects than those with high school, and those subjects with postsecondary education had no significantly elevated risk. This may indicate that persons living close to the emissions were also those of lower socioeconomic position, who may have higher susceptibility modified through workplace exposures, poor diet, and higher psychosocial stress (O’Neill et al., 2003).

Alternatively, effect modification could result from higher susceptibility rather than higher or more damaging exposure due to local point sources. The details of the analysis contained in the unpublished appendices of the Krewski report support a conclusion with results indicating subjects in the lowest education category had greater prevalence of occupational carcinogen exposure. The HEI reanalysis report (Krewski et al., 2000, Appendix B1) showed that the higher the education (high school, HS) level, the lower the exposure to known lung carcinogens at work (5.52% for <HS; 3.68 for HS; 1.61 for >HS). This may have contributed to the effect modification by education, rather than to the proximity to localized industrial particle sources which may have influenced the SO\textsubscript{2} confounding effect on SO\textsubscript{4}\textsuperscript{2-}. Possibly more workers exposed to occupational
carcinogens and having less education also live in areas with high SO2 concentrations.

In an effort to refine earlier ACS analyses, Jerrett et al. (2005b) analyzed the association between PM2.5 and O3 based on exposure gradients within the Los Angeles metropolitan area. Pollution exposures were interpolated with a geostatistical kriging model from 23 PM2.5 and 42 fixed-site O3 monitors. Proximity to expressways was tested as a measure of traffic pollution. Associations were assessed in standard and spatial multilevel Cox regression models. All cause mortality had an RR of 1.17 (95% CI: 1.05–1.30) for an increase of 10 µg/m3 of PM2.5, and an RR of 1.11 (0.99–1.25) with maximal control for both individual and contextual confounders. The RR for mortality due to ischemic heart disease (IHD) and lung cancer deaths were elevated, in the range of 1.24–1.6, depending on the model used. These PM results were robust to control for O3 and expressed exposure. Neither expressway exposure nor O3 exerted significant effects. The results suggest chronic health effects associated with intra-urban gradients in exposure to PM2.5 may be even larger than previously reported across metropolitan areas. Effects were nearly three times greater than in models relying on between-community exposure contrasts, and at least double when neighborhood confounding effects were taken into account. Much of the PM in the Los Angeles area comes from mobile source emissions, which may suggest these sources are more harmful to health although as the authors discuss, numerous other possible explanations for this doubling of the risk also may hold.

None of the intra-urban cohort studies has controlled for, or attempted to include, any microenvironmental exposure from the occupational setting, and control for copollutants was limited to crude markers of either gaseous or particulate exposure from government monitoring networks or from dispersion models with sparse data input. The binary road buffer used by Hoek et al. (2002) and Finkelstein et al. (2004) may confer exposure misclassification, as discussed, and makes it difficult to assess relative contributions from pollutants near roadways. Both studies presented evidence that residents living within 50 m of major roadways and within 100 m of expressways are more likely to die from cardiovascular disease than those living outside the road buffers. A subsequent paper by Finkelstein et al. (2005) indicates that industrial air pollution, measured as TSP and SO2, exerts an effect independent from the road buffers. The likely source of intra-urban variation is an industrial complex of steel mills, but associated diesel emissions from trucks that service the industry cannot be ruled out. This study is potentially important nonetheless because it reports significant associations to mortality from two likely sources: industrial emissions from steel mills, and transportation from road buffers. The findings on industrial emissions were thought to explain part of the inverse social gradient that is consistently observed between cardiovascular disease risk and social conditions in the neighborhood.

A Norwegian cohort study followed more than 16,000 men over 27 yr of age for 26 yr. Annual mean SO2 and NO2 levels were modeled for each residence with models taking traffic density into account (Nafstad et al., 2004). A total of 418 men developed lung cancer. Both in smokers and in nonsmokers, average home address NO2 levels were significantly associated with the adjusted incidence of lung cancer, but SO2 was not. The study suggests an impact from traffic sources compared to other PM particle or copollutant sources, but NO2 may also stem from heating sources. As emphasized in an accompanying editorial, the question is not “Does air pollution cause some lung cancers?” but “How many excess cases is it likely to cause?” (Cohen, 2003).

Although still formative, a pattern seems to be emerging from cohort studies that rely on within community or intra-urban exposure contrasts. Specifically, the observed health effects are much larger than in the earlier studies relying on between-community contrasts. The majority of these effects appear to be associated with traffic emissions, which imply that these sources are potentially more damaging, but the body of evidence still remains too small to draw definitive conclusions about the relationship between health outcomes and specific components of the pollutant mix, including those within PM.
led to an immediate and sustained improvement in air quality, following a ban of fuels used in Dublin, Ireland, in the fall of 1990. This intervention has been studied by both epidemiological assessment of health before and after the intervention. Such studies are rare for practical reasons. Moreover, the observation of effects may only be possible if the change in air quality is sufficiently large and immediate to lead to observable changes in health effects. Long-term effects of interventions on chronic health endpoints are inherently difficult to assess, given the many uncontrolled confounders that may also change in the long run, e.g., personal mobility or economic forces, affecting morbidity and mortality in the population. Thus, most intervention studies to date have focused on acute health effects.

**Intervention Studies**

In theory, the ideal study design to assess health effects of specific constituents or sources of air pollution consists of an intervention, where a defined change in air quality is accompanied with epidemiological assessment of health before and after the intervention. Such studies are rare for practical reasons. Moreover, the observation of effects may only be possible if the change in air quality is sufficiently large and immediate to lead to observable changes in health effects. Long-term effects of interventions on chronic health endpoints are inherently difficult to assess, given the many uncontrolled confounders that may also change in the long run, e.g., personal mobility or economic forces, affecting morbidity and mortality in the population. Thus, most intervention studies to date have focused on acute health effects.

Bituminous coal burning for domestic heating was entirely banned in Dublin, Ireland, in the fall of 1990. This intervention led to an immediate and sustained improvement in air quality (black smoke and SO$_2$ were markers). Clancy et al. (2002) showed that cardiorespiratory mortality was clearly lower in the 3 yr following the ban, as compared to the previous 3 yr. The study confirms that a ban of fuels used in Dublin led to reductions in mortality similar to, or larger than, expected from studies on acute and subacute effects of PM on mortality, such as NMMAPS and APHEA (Samet et al., 2000b; Katsouyanni et al., 2001). It is not possible, however, to assign these effects to specific pollutants or PM constituents.

Jaakkola et al. (1999) described the reduction in respiratory symptoms after regulatory interventions affecting a Finnish pulp mill as compared to a control region. Given that the interventions targeted a decrease in the malodorous (reduced) S (or mercaptans) compound emissions by 50%, the main changes in air quality related to reductions in the total S concentration. Although the findings are suggestive of a positive effect of the intervention, sulfur compounds may not be the only causal explanation, since odor-related effects of annoyance may lead to reporting of symptoms as well. The high levels of odorous pollution also limit the generalization of the findings to more widespread urban pollution.

A 1-yr closure of a steel mill in the Utah Valley is a widely cited intervention, and one that was studied by both epidemiological and toxicological investigations. This study confirms that a ban of fuels used in Dublin led to reductions in mortality similar to, or larger than, expected from studies on acute and subacute effects of PM on mortality, such as NMMAPS and APHEA (Samet et al., 2000b; Katsouyanni et al., 2001). It is not possible, however, to assign these effects to specific pollutants or PM constituents.

Another relevant series of studies accompanied the substantial and sustained improvements in air quality following the reunification of Germany. Declines of pollution in eastern Germany were particularly strong for SO$_2$. While the TSP declined as well, particle number concentrations did not change (Heinrich et al., 2000, 2002; Frye et al., 2003). The studies give convincing circumstantial evidence for declines in respiratory symptoms and improvements in lung function that paralleled a period of substantial environmental and social change. Experimental studies confirmed that PM collected in the early 1990s induced inflammatory responses (Schaumann et al., 2004). Pollution reductions in East Germany were complex, involving several sources. As noted by the authors, other pollutants were not monitored but may have paralleled the decline in sulfur. Energy from coal power plants decreased from 1991 to 1998 (Ebelt et al., 2001), remained stable for oil-based plants, and increased for gas powered plants. The number of vehicles increased strongly, but CO and NO$_x$ levels decreased. Accordingly, a specific source or pollutant assignment of causality goes, as with other studies, beyond the direct evidence supported by this study.

Also inconclusive with regard to causal sources or constituents is an early Italian study, where the intervention, that is, an improvement in air quality from 1980 to 1983, paralleled decreases in lung function of children (Aroso et al., 1987). SO$_2$ was used as a marker, but other pollutants were highly correlated during the period of decline in pollution. Avol et al. (2001) have shown that the intervention of moving from clean to polluted communities or vice versa leads to a decrement or increment in lung function growth, respectively. The findings are based on the participants of the CHS that moved to other locations all across the western United States. The PM of pollution used can neither be assigned to specific sources nor constituents.

A July 1990 intervention in Hong Kong limited the sulfur content of all fuel oil (for use in both power plants and vehicles). SO$_2$ and SO$_4^{2-}$ levels fell immediately; there was a 45% average reduction in SO$_2$ over 5 yr, while average SO$_4^{2-}$ levels were reduced by 15–23% for 2 yr before returning to preintervention levels after 2 yr. The other monitored pollutants (NO$_2$, O$_3$, and PM$_{10}^{}$) showed no clear declines. Respiratory health as well as mortality were monitored before and after the intervention (Hedley et al., 2002; Peters et al., 1996). Both the prevalence of respiratory symptoms and
cardio-respiratory mortality declined after the intervention. In particular, mortality peaks during the cool season were reduced in the first year. Although suggestive for reduction in effects of sulfur, the study also demonstrated some of the inherent difficulties in interpreting such interventions. The partly inverse trends in the pollution mixtures (e.g., an increase in O3 levels, difficulties in interpreting such interventions. The partly inverse trends in the pollution mixtures (e.g., an increase in O3 levels, slight declines in NO2, strong sustained decrease in SO2, and a decline and rebound of sulfate levels during the study period) complicate the assessment of the constituent-specific causality and may have hidden or misspecified the overall benefits of the intervention.

Similar limitations are particularly influential in an Austrian study, where NO3, total PM and SO2 all decreased from 1985 to 1990, although to different degrees both in the intervention and the control area (Neuberger et al., 2002). The reported indication of improved lung function in children cannot be assigned to specific sources or pollutants, and in the absence of other evidence, the study per se may in general not be conclusive.

In summary, intervention studies support a causal role of combustion-related air pollution on various health outcomes. Despite the high relevance and elegance of several of these studies, a broad generalization in terms of sources or PM constituents is not possible. Several findings are suggestive, but not conclusive, of a detrimental role of high sulfur fuel combustion, but it is common to all studies that (measured or unmeasured) copollutants may have been relevant as well.

COHERENCE BETWEEN TOXICOLOGY AND EPIDEMIOLOGY

This article aimed to provide a scientific basis using recent results from toxicological and epidemiological studies for evaluation of the coherence between these two disciplines concerning health inferences of ambient PM exposure as these may relate to specific PM characteristics. Epidemiological studies have focused on mortality or morbidity in toto, or specifically on respiratory or cardiovascular mortality/morbidity. Such studies have linked health effects to general indicators of PM, delineated by particle size and mass concentration; a few time-series design studies have investigated specific constituents, namely, SO4^2-, acidity, black carbon, EC, OC, metals, and crustal materials. However, the question of which PM characteristics or constituents play specific pathophysiological roles cannot be adequately investigated solely with epidemiological studies, which are faced with often intercorrelated atmospheric chemistry observations. Thus, toxicological studies using controlled exposure designs must be a component of any integrated evaluation of PM components associated health outcomes. Toxicological studies relate to specific biological endpoints following exposure to PM surrogates or CAPs that may serve to describe mechanisms underlying adverse health outcomes; these have commonly included inflammation, oxidative stress, or alterations in cardiovascular function. Despite the inherent differences in approach taken by these two disciplines, including use of often divergent health endpoints, the recent literature does show certain commonalities. On the other hand, there are also important differences, or perhaps inconsistencies, in the results that require reconciliation.

An integration of results from the two disciplines, based on details presented in previous sections of this article, can be organized in different ways, such as by health endpoints or by physicochemical descriptors of PM. Since current policy for managing air quality focuses on PM particle size, physicochemical descriptors along with source knowledge are used as the basis for the discussion in this section that serves to illustrate coherence or divergence in toxicological and epidemiological inferences. Details of studies are excluded, since these have been provided elsewhere.

PM Size Mode

Toxicological studies have shown that all size modes may result in biological responses that could be mechanistically related to health outcomes seen in epidemiological studies. Epidemiological studies of acute and chronic health effects suggest that the fine particle mode, which incorporates ultrafines, is related to health outcomes. However, there is insufficient data from epidemiology for either ultrafine PM alone or coarse PM to draw any firm conclusions about health effects from these size modes specifically, that is, without regard to particle chemistry. Furthermore, biological responses to PM in any of the size modes may not always be linked with major constituents but rather with toxicologically potent minor components.

Modern combustion processes, including internal combustion engines, produce particles in the ultrafine and fine modes, strongly influenced by carbon. Toxicological and epidemiological studies historically have supported PM regulation in terms of the fine and coarse modes (e.g., U.S. EPA, 2004). Recent toxicological studies have focused on the ultrafine fraction, and these suggest a potential importance in biological responses to PM. Thus, it appears that the smaller the particle size, the more potential there is for adverse health effects to be observed. Although ultrafine particles generally contribute little to ambient PM mass concentration, they do influence the specific surface area as potential carriers of adsorbed toxic components. While recent epidemiological studies, including studies of proximity to traffic sources, have not used ambient ultrafine PM data, they have shown that populations near major roads are more susceptible to adverse health effects than are those living farther away. Since ultrafine particles can derive from motor vehicle exhaust, these studies may implicate such particles to health outcomes. However, the toxicological basis for any such linkage is qualified, in that findings to date generally do not necessarily distinguish between chemical composition differences by size, versus size in itself, with the exception of PAH studies in Los Angeles (Li et al., 2002b, 2003). Furthermore, the epidemiological traffic proximity studies do not preclude the influence of fine particles, chemical components such as PAH, or synergism with traffic-related gases, such as CO, VOC (or SVOC), and NOx.
There is evidence that spontaneous, secondary sulfuric acid nucleation occurs from \( \text{SO}_2 \) oxidation, producing transient “bursts” of ultrafine particles under certain conditions. Although the possible health significance of these particles has not been investigated, they involve low mass concentrations of acid and are believed to be short-lived, so are unlikely to be a factor in adverse health outcomes. However, further study may be required depending on the \( \text{SO}_2 \) source, which may include industry, power plants, or localized motor vehicle emissions.

**PM Chemical Composition**

Toxicological investigations have indicated that it is not solely total mass concentration of ambient PM that relates to every observed biological effect but rather that specific chemistry is clearly a factor in this regard. Differentiation by chemical composition is likely to be most compatible with traditional toxicity measures, and chemical components serve as potentially unique source tracers for PM. In the following, key PM chemical components are used to assess the coherence or disparity between toxicology and epidemiology.

**OC, EC, and Biogenic PM**

While laboratory-based studies have indicated that as a group the organic constituents of PM are likely to be toxicologically active (Urch et al., 2004), speciated OC and EC fractions of ambient fine PM have not been well characterized in terms of health impact mechanisms. One class of carbonaceous material having health concern seems to be PAH (e.g., Somers et al., 2004). For example, mice exposed to PM-polluted air from a steel mill in Hamilton, Ontario, showed evidence for increased mutagenicity compared with mice exposed to air 30 km away; the former site had levels of PAH that were about 33 times greater than those at the latter site, although there was no mention of differences in concentration of metals. Evidence also suggests that carbon particles can serve as cores onto which other adsorbed chemical species are present, complicating toxicological interpretation of responses to carbonaceous material. Biogenic material such as endotoxin, found mostly in coarse particles, is a known toxic agent, and other biological debris may initiate allergic reactions.

Epidemiological studies generally have not dealt extensively with the carbon fraction of PM. One study, for example, suggested associations with carbon or soot and vehicle gas exhaust in Atlanta, GA (Metzger et al., 2004). Factor analyses combined with time-series analysis have inferred an indirect connection, using Pb as a marker for pre-1980s motor vehicle exhaust (Laden et al., 2000; HEI, 2003) or CO and NO\(_x\) associations, with these latter being surrogates for vehicle exhaust that likely includes carbonaceous PM. Roadside emissions of CO and NO\(_x\) have been implicated in a study of mortality in Phoenix. Proximity studies investigating intracity gradients and proximity to traffic sources indirectly implicate OC and EC, as well as other motor vehicle emissions, in adverse health outcomes. These studies also may implicate carbon as a major component of ultrafine PM, but this is yet to be confirmed. Times-series studies suggest that acute exposure to EC and OC components of PM may be associated with greater effects than that associated with total fine PM for both cardiovascular hospital admissions and mortality (Metzger et al., 2004; Mar et al., 2003).

Thus, both toxicological and epidemiological studies have indicated that some OC constituents of PM are likely to be related to adverse health outcomes. While existing data are not sufficient to develop unequivocal conclusions about health hazards from specific organic compounds, the best current candidate is PAH, or its nitro and oxy derivatives. However, there is currently little in the epidemiological database to determine the extent of any coherence with toxicology related to specific OC components of ambient PM.

**Secondary PM Species—Sulfate**

Secondary Sulfate as an acid or an ammonium salt, found mainly in the fine fraction of PM, has probably received the most attention of all of the PM components in terms of its potential for adverse health effects. Primary PM metal sulfate derives from combustion of residual oil, for example, but the bulk of SO\(_4^{2-}\) in ambient PM is generally secondary. A recent review of toxicological evidence indicates that SO\(_4^{2-}\) per se has little or no effect on health, with any effects appearing to be related to the acidity of the specific compound containing SO\(_4^{2-}\) (Schlesinger & Cassee, 2003). However, primary SO\(_4^{2-}\) PM emissions may contain water-soluble transition metals, creating a mixture that may have toxic properties, as suggested by Grahame and Hidy (2004). In a subchronic CAPs exposure study, for example, Maciejczyk and Chen (2005) noted that secondary SO\(_4^{2-}\) (and OC) constituted 65% of the PM mass, but were not associated with significant biological effect.

Time-series studies investigating the role of sulfates have frequently reported small and statistically insignificant effects, while chronic studies on long-term effects have reported relatively large associations. Sulfates have significant associations with all-cause mortality as well as with cardiovascular and lung cancer mortality in the largest studies investigating chronic exposure. These effects were evaluated using between-city exposure contrast, and the associations were robust to control for numerous risk factors (Pope et al., 1995, 2002; Krewski et al., 2000), although they were confounded by the precursor gas sulfur dioxide (Jerrett et al., 2003). In contrast, Metzger et al. (2004) used a time-series design and did not implicate SO\(_4^{2-}\), but instead focused on CO and carbon species.

Only a few factor/time-series analyses have been done, and these yielded mixed results, with SO\(_4^{2-}\) generally showing small or insignificant effects. The six (Eastern–Midwestern) cities analysis originally reported an association with a regional coal factor, which evidently was driven by results for Boston (Laden et al., 2000). Subsequent analyses of these data suggested the coal combustion association to be insignificant (HEI, 2003). Results from the Phoenix area suggested a link between mortality
and SO₂, and a weak association with SO₄²⁻, but did not distinguish between regional SO₄²⁻ from smelter emissions and electricity generation. An intervention study conducted in Hong Kong has also provided insight about the role of reduction in SO₂ emissions resulting from the reduction in sulfur content of residual fuel oil and diesel vehicle fuel. This fuel switching was accompanied by major reductions in SO₂ and SO₄²⁻ and a reduction in mortality over a period of a few years. Reductions in the amount of ROFA produced and/or in the metal content of ROFA as the residual oil S content was reduced may also have been a factor in the results, but this was not discussed by the investigators (Thurston & Spengler, 1985). Reductions in the amount of ROFA emitted and/or its metal content as residual oil sulfur content was reduced have reportedly taken place in the Boston area, for example. Accounting for this, or other changes in pollutant chemistry, could have influenced the results reported by Thurston & Spengler (1985) and Laden et al. (2000).

Reasons for the apparent lack of coherence in SO₄²⁻ results between toxicology and epidemiology are unclear, but may relate to a number of factors: lack of distinction between secondary SO₄²⁻ and primary metal-sulfate components; differences between the form of SO₄²⁻ used in toxicology and that found in ambient air; and interactions between SO₄²⁻ and other PM constituents in producing adverse health effects. The use of central area air monitoring in cohort studies and the limited measurements in these studies could result in effects ascribed to SO₄²⁻ that may actually have been due to co-correlated, but unmeasured, components. Addressing this and other apparent contradictions necessarily will require heightened emphasis on longer term toxicological and epidemiological studies that use more personal monitoring to ensure exposure consistency between subjects and among PM constituents.

Trace Metals

Toxicological studies strongly suggest that transition metals, such as V, Fe, Ni, Cr, Cu, Zn, and Mn, are components of PM with toxic potential, although the relative toxicity of water-soluble versus insoluble forms is not clear. The mass concentration of transition metals in ambient PM varies widely geographically in the United States but is generally quite low. On the other hand, toxicological experiments have generally been conducted using metal concentrations much higher than levels found in ambient air. However, a recent subchronic exposure study to CAPs suggests that biological effects may occur at the low metal concentrations, specifically for V and Ni, present in the atmosphere (Maciejczyk & Chen, 2005).

Epidemiological studies have generally been silent about the role of metals, except perhaps in some of the factor analyses (Laden et al., 2000; HEI, 2003) and the residual oil findings of Grahame and Hidy (2004). However, the intervention study in the Utah Valley is instructive in this regard. Reduction in metals (e.g., V, Fe, Cu, Zn, Pb) in PM associated with closure of a local steel mill apparently resulted in improved health conditions in the local population. The Hong Kong intervention study also may have implications here. A reduction in residual oil combustion and resulting declines in mortality could be related to reductions in SO₂, secondary SO₄²⁻, sulfur from diesel fuel, or in metal sulfates from residual-oil-fired plants. On the other hand, a panel study to assess the role of metals in exacerbating respiratory symptoms showed insignificant results (Roemer et al., 2000). Thus, overall, there is an insufficient database to determine whether there is coherence between toxicology and epidemiology related to the role of trace metals in adverse health outcomes from ambient PM.

Crustal Materials and Soil Dust

Ambient PM₂.₅ contains soil dust as measured by crustal elements, such as Si, Ca, Al, or Mg. Coarse-mode PM generally contains a substantially larger fraction of such crustal material than does fine PM. However, this naturally occurring crustal material may be contaminated with road dust produced by moving vehicles. This latter may contain a variety of material, including OC (e.g., PAH) and various metals, such as Pb and Zn, that may modify the toxicology of the naturally occurring crustal components (Glaser et al., 2005). Toxicological studies using high concentrations of crustal material have shown contradictory results, which range from little or no significance to implicating markers such as Si, assumed to derive from soil or road dust, as potential health hazards.

Epidemiological studies specifically identifying soil dust as a component of fine PM (via factor analyses) in the Six Cities and Phoenix studies have suggested that this type of PM is not a significant health hazard. Given these results, wind-blown dust, at least in rural areas, probably has a lower priority for further investigation than other, less well studied, components, such as the carbon fraction. The database for health effects from crustal materials is not sufficiently robust to allow evaluation of coherence between toxicology and epidemiology.

Coherent Conclusions

The toxicological database continues to support the hypothesis that it is unlikely that any single physicochemical property of PM is responsible for all adverse health outcomes reported in epidemiology studies. Since the relative toxicity of various components of PM probably differs for different biological endpoints, it follows that the influence on public health from each of these components is unlikely to be the same in different geographical regions where the physicochemical properties of ambient PM may differ.

Through their various study designs, epidemiological investigations offer an increasingly important opportunity to examine PM attributes (and therefore sources) that can be complemented with toxicological studies, with these latter being capable of identification of broad source classes using CAPs and factor analysis. Incorporation of receptor modeling through factor
analysis with factor regression analysis has added important insight about health impacts of PM constituents. Yet, with the possible exception of pollutants from motor vehicles, epidemiology has not as yet been successful in the unambiguous constituent- or source-specific evaluation of health risks, although incorporation of receptor modeling by factor analysis has added insight into PM origins. Even in the case of motor vehicles, ambiguity lies in the distinction between the potential effects of fine PM, ultrafine PM, OC, EC, or pollutant gases, including SVOC.

In drawing on both current source-specific and physicochemical evidence concerning PM characteristics and health effects, and accounting for the many uncertainties involved, the following overarching conclusions may be reached:

- Smaller particles generally appear more closely associated with adverse health outcomes than do larger ones. Evidence on acute and chronic effects identifies fine fraction ambient PM with larger health effects than the coarse fraction, or than TSP. Evidence on ultrafine particles remains too formative to draw firm conclusions about health effects from ambient exposures specifically to this size mode.

- Traffic-related sources appear closely associated with health effects. This may not, however, reflect the true relative impact on health, but rather the relative lack of studies focusing on other sources. Furthermore, particles having “traffic” origin often appear in “bundles” of other pollutants, especially gases, and either independent or synergistic effects from other pollutants that appear in these bundles cannot be unequivocally ruled out. For example, there is toxicological evidence indicating synergism between NO₂, O₃, and PM (Kelly, 2003).

- Emerging studies using proximity measures and intra-urban exposure contrasts appear to provide evidence for larger effects from this exposure gradient than from earlier studies using between city contrasts. This seems to hold, with a few exceptions, across the cross-sectional, case-control, and cohort-study designs.

- Increasing evidence seems to implicate PM in the development of serious chronic diseases rather than merely in the exacerbation of symptoms of pre-existing disease states. The Children’s Health Study on childhood lung function deficits (Gauderman et al., 2004) and a recent study on atherosclerosis (Kunzli et al., 2005) both support a “development of disease” hypothesis, aside from the fact that the study location in Southern California implicates transportation sources as the main contributor to ambient PM concentration.

**FUTURE DIRECTIONS**

The discussion in this article demonstrates that, in spite of major research efforts in both toxicology and epidemiology, the issue of relative contribution to health outcomes of specific properties of PM and, therefore, of specific sources is not resolved. As noted by the NRC Committee on Research Priorities for Airborne Particulate Matter (NRC, 2004), key questions about the role of components of PM require “a carefully . . . coordinated, long-term multidisciplinary research effort . . . that goes well beyond the work now under way.” The ideal research task would involve a matrix, “with particle characteristics as one dimension and health outcomes as the other.”

Most epidemiological studies have not focused on identifiable sources, and have used only a few markers of PM. Those that have used more than one marker are almost all in the acute exposure domain. The most definitive evidence about sources comes from some of the most basic measures of exposure, namely proximity in time and space. Time-series studies exploit short time windows to assess likely contributions from traffic and other sources, while proximity studies utilize small-area exposure windows close to the source to determine the likely association.

In parallel with these small-area studies, researchers will have to do more to understand the influence of multiple particle constituents in different source-influenced environments, including traffic. For example, the most intensive studies dealing with the distance decay in various physicochemical PM constituents focus on large highway sources (Zhu et al., 2002a, 2002b), yet little is known about how these mixtures change in densely populated urban areas with street canyons, complex terrain, or meteorological conditions. It is difficult to disentangle the contribution of specific pollutants or constituents to these findings among the numerous primary PM from motor vehicle exhaust, SVOC, and secondary PM with highly correlated spatial gradients within 0–100 m of roadways. One Dutch study reported a 30% PM₁₀ elevation near roadways compared to background sites (Fischer et al., 2000). Studies in the northeastern United States demonstrated a doubling of indoor PM₂.₅ at high traffic locations compared to low traffic areas (Levy et al., 2001), and higher levels of diesel particulates in areas with truck traffic (Lena et al., 2002). More work of this kind will be needed to interpret the health effects of proximity, and the likely contribution of PM to observed effects.

Along a similar vein, toxicology studies, using comparable research protocols and biological endpoints, are needed that use different pollutant mixtures to determine which components may be more harmful, or less so, when examined in such a comparable basis. This can include, for example, studies of CAPs in different regions, but comparing responses only at concentrations relevant to these regions. Multivariate component analyses can enhance such intercomparisons. However, one must bear in mind that, ultimately, it is the deposited dose that determines any response, and thus a critical goal of toxicological studies needs to be characterization of the actual dose from inhalation of PM components at specific exposure concentrations. Such characterization is rarely performed in contemporary toxicological evaluations.

A focus on source-specific constituents ultimately requires approaches that take spatial variation of human exposure into
account. It is insufficient to attribute pollutants measured at only one monitor or averaged over a few monitors to human exposure over a broad area and thus to understand the health relevance of sources and compositions. As shown in various studies, monitor-to-monitor association and monitor-to-personal exposure correlation largely differ across constituents, and consequently the precision and errors in assigned “exposures” also differ. While PM mass measurements may not vary much across a city, personal exposure to a range of pollutants from different sources can vary by up to an order of magnitude within a few hundred meters of these sources.

As a result of the financial constraints placed on most air pollution studies, only a few have examined the use of personal data for modeling of health effects. While studies such as RIOPA (Meng et al., 2005) and EXPOLIS (Jantunen et al., 1998; Koistinen et al., 2004) have explored various relationships between ambient, indoor and personal exposures, only a few panel studies have actually used personal monitoring data. Arguably, if society wants to understand which constituents and sources of particles are most harmful, much greater collective investments may be required to comprehend how the exposure equality criterion is met for different particle constituents. Major projects, such as the $30,000,000 study to investigate atherosclerotic disease with the Multiethnic Cohort for the Study of Atherosclerosis recently funded by the U.S. EPA, may be needed to understand the contribution of selected sources. Studies such as this, with extensive personal and indoor monitoring programs, may begin to resolve some of the apparent “discrepancies” in coherence between toxicological and epidemiological studies of PM-related health effects. In the absence of major studies of this kind, opportunities now exist to take advantage of contemporary monitoring network data. These include: (1) PM$_{2.5}$ composition from the U.S. EPA speciation network, which encompasses most of the properties listed in Table 1; (2) the U.S. EPA supersite network data, which cover ultrafine particle concentrations, trace gases, and some speciated OC and SVOC data; (3) speciated VOC and NO$_x$ data from the U.S. EPA PAMS network, which includes major species of carbon number less than 12; and (4) other networks operated for many years in Canada, and specialized PM–trace gas networks in the southeastern United States, like the Southeastern Aerosols Research and Characterization project (SEARCH).

Regardless of the specific research tasks ahead, an immediate need exists for publication and reporting guidelines that will assist in study designs through improvements in tracking or codification of health effects in association with physical and chemical characteristics of monitored particles. No coordinated enterprise has been undertaken to understand the toxicity from different particle constituents and size fractions. This includes the use of various protocols in toxicological studies, resulting in difficulties in comparing results even using the same type of PM across different investigations. The same problem is true of epidemiological studies. Modest advances have been made toward understanding the relative health impact of different particles, but a more systematic approach is required. The toxicological and epidemiological studies need to be better integrated such that information from one may be used to assist the other.

The beginnings of such an approach may lie in standardized publication and reporting guidelines that facilitate easy tracking and comparison of results. For example, comparison of clinical trials is made possible by the CONSORT (Consolidated Standards for Reporting Trials) statement to improve the quality of reporting results of a randomized control trial (Begg et al., 1996). This statement is a widely adopted requirement for medical journals (Moher et al., 2001). While the World Health Organization (WHO) has developed a suggested protocol for conducting health impact assessments that specifies purpose, approach, assumptions, methods, metrics, and estimations, it does not outline how to report results for easy comparison and compilation (WHO, 2000). Although such a standardized approach will require much consultation among researchers and policymakers, the development of a reporting framework similar to CONSORT will be necessary to track and understand the relative health burden from particles of different sizes and made up of different constituents.

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