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Evaluating the Health Risk from Secondary Sulfates in Eastern North American Regional Ambient Air Particulate Matter

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Epidemiological studies of particulate matter (PM) using central area monitors have associated total PM mass, as well as certain individual components of PM, including sulfate, with adverse human health effects. However, some recent studies that used concentrated ambient particles (CAPs) or analyzed the effects of air pollution from different sources or geographic areas suggest that while some particles may be harmful, other particulate species including secondary sulfates may have negligible health effects. Toxicology studies to date also suggest that secondary sulfates pose little health risk. While studies using central-area monitors implicitly assume that all residents of the area are exposed to the same levels of pollution, newer studies find substantial health effects for those in close proximity to major roads. These latter studies recognize that although population exposure to widespread pollutants, such as total PM mass and sulfates, may be relatively uniform over a wide area, exposure to pollutants from local sources is not. While there is an emerging literature associating several adverse health effects with proximity to local pollution sources, the current database provides limited information that allows identification of specific particulate species that may cause little to no harm. In this article, we suggest that ambient secondary sulfates, and eastern North American regional air masses generally, appear to have little adverse impact on public health. This suggestion is based on evidence gleaned from eight avenues of investigation: (1) recent non-central-area monitor studies, including exposure gradient or proximity studies; (2) CAPs studies; (3) studies that examine effects related to different geographic areas or sources; (4) toxicology studies; (5) the limited number of studies that analyze existing central-area monitor data to explicitly examine the health impacts of sulfate and acidity versus PM mass; (6) "modern" area monitor studies with additional capabilities to distinguish among sources of pollution; (7) partial reinterpretation of two pivotal cohort studies; and (8) studies separating effects of secondary sulfates from those of primary metal sulfates. However, uncertainties remain regarding the role that secondary sulfates may play in ambient PM chemistry pathways leading to potentially harmful products, such as the possible effects of secondary organic aerosols that may be the product of acid catalysis of sulfur dioxide. Thus, more targeted study is needed, and some research suggestions are made in this regard.

Associations between both acute and chronic adverse health effects and ambient particulate matter (PM) mass concentration have been widely reported (e.g., Dockery et al., 1993; Goldberg et al., 2001; Pope et al., 1995, 2002). In particular, fine particles ($PM_{2.5}$; particles less than 2.5 μm in diameter) have been linked extensively with morbidity and mortality outcomes (e.g., Schwartz et al., 1996; Lippmann et al., 2000; Gold et al., 2000). Virtually all of these epidemiological studies utilized averaged data obtained from central-area monitors.

Many such studies also found associations specifically with sulfate. This isn't surprising, because sulfate is the chemical species that accounts for the greatest single fraction of PM2.5 in regional air masses in eastern North America; in the United States, sulfate mass concentrations range typically from 4 to 7 $\mu g/m^3$ from northern Florida through the Midwest, while

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nitrate levels are typically below 1 $\mu g/m^3$ in those areas (U.S. EPA, 2001). While most sulfate is secondary, formed by the oxidation of SO_2, primary metal sulfates from local sources, such as smelters and sources burning residual oil, can also be important in some areas.

Does a common finding between adverse health outcomes and PM mass in studies performed in various regions mean that all $PM_{2.5}$ is relatively equally toxic? Many scientific bodies and scientists believe that different constituents of $PM_{2.5}$ are likely to have different toxicities, and have called for research to distinguish which types are most or least harmful (CASAC, 1996; NRC, 1998, 2004; Ware, 2000; Mittleman & Verrier, 2003).

Most recently, a report from the National Research Council Committee on Research Priorities for Airborne Particulate Matter (NRC, 2004) states, "The current National Ambient Air Quality Standards (NAAQS) for PM are based on size and mass and assume that all particles have the same toxicity per unit mass irrespective of chemical composition. In the committee's judgment, that assumption greatly oversimplifies complex biological phenomenon . . . [and] there are studies suggesting that health impacts of sulfate *per se* may not be proportional to their contribution to ambient PM mass." In this article we explore this last point more fully.

Recognizing that correlation and causation are not the same, the findings of PM studies using central area monitors are consistent with the following three paradigms:

1. All types of $PM_{2.5}$ have relatively equal toxicity, because total $PM_{2.5}$ mass has been reported to positively correlate with rates of mortality, hospital admissions, and respiratory morbidity.
2. Some components of $PM_{2.5}$ mass having specific physicochemical properties are more toxic than are others, but these are all too highly correlated with each other to differentiate easily.
3. $PM_{2.5}$ (or PM_{10}) acts as a proxy for local pollution sources, including locally produced ultrafine PM, which vary strongly within a major city but which are the most toxic types of air pollution. This is because central-area monitors measure variations in PM mass and sulfate representatively, because both are widely distributed with relatively little regional variation, but measure variations in pollution from local sources such as major roads and large industrial sources poorly because pollution from these sources can vary by an order of magnitude within a relatively short distance from the monitor.

This article explores these three paradigms, arguing that current evidence favors the latter two viewpoints, which, depending on the pollutant, are not necessarily mutually exclusive. We suggest that while exposure to ambient air in close proximity to major roadways and some major industrial sources appears harmful, exposure to $PM_{2.5}$ from regional eastern North American air masses, dominated by secondary sulfates, appears to have relatively minor or negligible toxicity.

HEALTH EFFECTS FROM LOCAL EMISSIONS: NON-CENTRAL-AREA MONITOR STUDIES

Given epidemiological findings of consistent health effect associations with fine PM, it is first necessary to review which types of PM might cause such health impacts. This section reviews evidence pointing toward the most widespread of local emissions, namely, those from motor vehicles and near roads; such emissions can vary by a factor of 5 to 10 within 150 m of a major highway (Zhu et al., 2002a, 2002b). Later sections review the evidence suggesting that eastern North American regional air masses generally (which average 25% to 35% secondary sulfate on an annual basis) and secondary sulfates specifically appear to have relatively benign health impact.

There is now ample evidence that local ambient exposure conditions likely have a significant impact upon health outcomes. Many studies, conducted in both the United States and Europe, reported significant associations between adverse respiratory health effects and close proximity to major roads, especially those with large numbers of diesels; these health effects rapidly decreased as distance from highways increased (e.g., Venn et al., 2001; Lin et al., 2002; Janssen et al., 2003; English et al., 1999; Buckeridge et al., 2002; Nicolai et al., 2003; van Vliet et al., 1997; Brunekreef et al., 1997). Although these studies examined different endpoints and used somewhat different methodologies, the results of the Lin et al. (2002) study are generally illustrative. The authors found the odds ratio for childhood asthma hospitalization almost doubled for children living in closest proximity to heavily trafficked roads, especially those having high volumes of trucks and trailers.

A study in the Netherlands of chronic health effects of emissions (Hoek et al., 2002) examined the relationship between premature mortality and distance of residence from major roads. People aged 55 yr and older and living within 100 m of a major highway or within 50 m of a major urban road had almost double the risk of cardiopulmonary mortality than did those living further from roadways. For all-cause mortality, the relative risk was 1.53 and was statistically significant for the "living near major roadway" mortality variable when the association was derived for those living at their initial address for 10 yr or longer. This suggests a chronic effect of living near a major roadway. The authors found nearly identical associations between risks of higher mortality and both black smoke and nitrogen dioxide levels, but did not attribute the excess mortality to any specific pollutant(s); they did, however, point out that ultrafine PM levels are much higher very close to highways.

A study in Los Angeles (Mann et al., 2002), found a 1 ppm increase in estimated 8-h CO levels to which a person was exposed at their home to be significantly associated with an increase in hospital admission for ischemic heart disease (IHD) for those with a secondary diagnosis of either congestive heart failure (CHF) or arrhythmia (ARR). The authors attributed the

health effect to highway emissions generally, since CO levels rise and fall with levels of other particulate and gaseous emissions from vehicles, in relation to proximity to the major roadway. However, the PM mass measure in this study (PM_{10}) was not significantly associated with adverse health endpoints. The authors concluded that people with IHD and accompanying CHF and/or ARR constituted a sensitive subgroup in relation to the effects of air pollutants associated with motor vehicle combustion.

The level of the adverse health effect is likely understated in the study just described because there was less precision in relating exposure site to monitoring site than that in the study of Hoek et al. (2002). In the Mann et al. study, CO, NO_2, and PM levels to which a person was assumed to be exposed were interpolated relative to the center of the ZIP code in which hospital admittees lived, based on the location of the nearest two of 25 to 35 monitors in the Los Angeles area. Certainly, many of the homes would have been located in areas more than several hundred feet from a major highway, while others would have been very close to the highway and therefore would have interpolated CO levels much lower than those to which the location was actually exposed.

Tarkiainen et al. (2003) found an association between CO concentration and increases in r-MSSD in patients with coronary artery disease, suggesting increased vagal control during CO exposure. The exposures were divided into low (<2.7 ppm CO) and high (>2.7 ppm CO) groups; the change in heart-rate variability (HRV) was found only in the latter (CO range = 0.5 to 27.4 ppm). In this group, 23 of the 30 episodes were related to traffic, so there remains the possibility that traffic emissions other than CO might have caused the change in HRV. Implied from results of this study is that heart-rate variability appeared to be unaffected in areas with low vehicular or CO emissions.

Results of the studies just described are similar to those of two studies of heart disease in bridge and tunnel workers in New York. Stern et al. (1988) reported an elevated risk of arteriosclerotic heart disease among tunnel officers as compared with bridge officers; vehicular emissions were higher among tunnel officers as measured by CO concentration. The risk declined after cessation of exposure, with much of the risk dissipating within as little as 5 yr after cessation. Thus, the exposure gradient in this study was length of time working near a roadway. Herbert et al. (2000) reported that coronary heart disease (CHD) was strongly associated with duration of occupational exposure, with CHD prevalence increasing in a stepwise fashion with length of service.

STUDIES USING CONCENTRATED AMBIENT PARTICULATES

Some indication of specific PM properties that may be responsible for adverse health outcomes of interest has been provided by controlled exposure studies that have attempted to simulate ambient PM exposure by use of concentrated ambient particulates (CAPs). Godleski et al. (2000) examined electrocardiograms (ECGs) in dogs exposed to concentrated ambient particulates (CAPs) in Boston. The researchers found that CAPs-exposed animals showed a shortened time to ST segment elevation and an increased magnitude of the ST segment, compared to controls. Changes in heart-rate variability and decreases in T-wave alternans were also reported. On about one-fourth of the days, there were no adverse effects. Using back trajectories of the air masses on days with and without effects, the authors noted that on a day with increased cardiac effects mediated by the vagus nerve the wind was from the the northwestern direction and was low in sulfates, while on a day with no effect the wind was from the southern direction and was higher in sulfates. Comparing levels of trace elements on these different days, the day with no effect had 11 times more selenium and about 50% more sulfate, implying a coal source with secondary sulfates. On the day when the wind was from the northwest and adverse effects were found, vanadium (V) and nickel (Ni) levels were higher.

While the authors did not attempt to assign toxicity to any particular source, they did state, "The failure to respond resulted from a lack of toxicity of the actual exposure rather than to a non-responsive animal." These results suggest that for the observed endpoints, if a PM type (or types) is (are) absent from the air or below a threshold, no effects will be triggered, and that secondary sulfate levels can be high on days showing no adverse health effects, implying a lack of a role for this chemical species in this regard.

A later study (Wellenius et al., 2003) examined the effect of CAPs on myocardial ischemia in a canine model of coronary artery occlusion. The authors found that exposure to CAPs significantly enhanced occlusion-induced peak ST-segment elevation, but found that of the four tracer parameters examined [Ni, S, black carbon (BC), and Si], only Si showed a significant association with changes in ST-segment elevation and heart rate. The authors interpreted this finding to mean that components of urban street dust may have caused the effects. Although the S tracer was not associated with any cardiac effect, the total mass was higher for the S tracer (254.15 $\mu g/m^3$) than for the Ni (37.01 $\mu g/m^3$), BC (52.33 $\mu g/m^3$), and Si (115.44 $\mu g/m^3$) tracers. This finding of high mass associated with the S tracer is similar to that found in Godleski et al. (2000) on a typical "no-effect" day.

Brook et al. (2002) exposed healthy humans to CAPs ($\sim$150 $\mu g/m^3$) plus ozone ($\sim$120 ppb). The combined exposure caused a significant brachial artery vasoconstriction, compared to filtered air inhalation; while this effect is unlikely to harm a healthy young adult, it could promote a cardiac event in older people having already narrowed arteries. The authors pointed out the substantial evidence suggesting links between PM and cardiac mortality, but could not exclude, on the basis of this study, a partial effect due to ozone. However, the CAPs were obtained from a location within 100 m of a major road in downtown Toronto (personal communication, R. Brook). These

findings suggest that the effects could be due to PM from vehicular emissions, consistent with highway proximity studies already discussed and toxicology studies discussed later.

HEALTH EFFECTS RELATED TO PM FROM SPECIFIC GEOGRAPHICAL AREAS OR REGIONAL SOURCES

Three recent studies allow a comparison of the health effects associated with rural air masses, which contain aged emissions, including secondary sulfates, with the effects of urban or industrial emissions. Although each study evaluated different health endpoints, the rural air mass had no association with adverse health outcomes in any.

Somers et al. (2004) found that mice exposed to emissions from an industrial/urban area in Canada showed twice as many heritable mutations as did mice exposed to cleaner rural air. Reduction of urban/industrial PM (with HEPA filters) sharply lowered the risk of heritable mutations, but filtering the rural air did not affect the mutation rate. The researchers found that weighted daily average exposures of mice to polycyclic aromatic hydrocarbons (PAH), which are known mutagens and carcinogens, were 33 times higher at the urban/industrial site than at the rural site, a far larger disparity than for PM concentration. The HEPA filters removed at least 55% of the PAHs, and perhaps as much as 100%; in part because of this degree of uncertainty, the authors couldn't make conclusions about the importance of PAHs for the effects found.

Creason et al. (2001) examined changes in heart rate variability among 56 elderly, nonsmoking residents of a retirement center in Baltimore Country, MD. Using data for all 24 days, the authors found a small, nonlinear ("U"-shaped) response to rising PM levels. When data for 2 days were removed, data for the remaining 22 days showed a larger, linear, significant negative association between $PM_{2.5}$ and heart-rate variability. The authors state that the $PM_{2.5}$ on the 2 days removed from the analysis "clearly did not exhibit the same association with HRV as the other study days," and derived from different sources and had different composition than did PM on the other days. The air mass on these two days was from rural Pennsylvania, while on the other days the air mass was from either urban areas or the industrial Midwest. On these 2 days, PM levels, as well as sulfate levels, were high compared to the other 22 days. The findings of Creason et al. (2001) are, thus, consistent with those of the two CAPs studies (Godleski et al., 2000; Wellenius et al., 2003), neither of which found adverse effects on days when S and PM mass were higher than on those days when effects were found.

Similarly, Gent et al. (2003) found no association between regional $PM_{2.5}$ concentrations and respiratory symptoms in asthmatic children. The children were drawn from a 6691-square-mile area in Connecticut and central Massachusetts, a mostly suburban and rural area surrounding Hartford, CT, and Springfield, MA. The air quality data were from a number of monitoring sites within about 50 miles of Southington, CT (14 miles southwest of Hartford). Significant associations were found between elevated ozone levels and respiratory symptoms and use of rescue medication for children using maintenance medication, but no associations were found for $PM_{2.5}$. Addition of same-day sulfate, a primary constituent of $PM_{2.5}$ in the region, to the ozone model did not alter the results.

TOXICOLOGY

This section briefly reviews toxicological evidence that supports the contention that sulfates play only a minor, if any, role in epidemiological associations between fine PM and adverse health outcomes, and that vehicular emissions likely play a more significant role in this regard.

Toxicology of Secondary Sulfates

Schlesinger and Cassee (2003) reviewed toxicological studies on secondary sulfates, concluding that such particles are unlikely to be harmful at environmentally relevant levels.

Toxicology of Vehicular Emissions: Coherence with Epidemiological Health Outcomes

A fairly substantial database exists for the toxicology of vehicular emissions. Some early studies examined whether CO might cause acute health problems at previously ambient levels, which were approximately 20 to 40 times higher 20 to 30 yr ago. More recent studies have examined diesel emissions, ultrafine PM, and vehicular-derived components of CAPs.

Carbon Monoxide

CO is highly correlated with highway $PM_{2.5}$ emissions and thus is a proxy for such emissions, but it also may be potentially responsible for a portion of the adverse health effects attributed to vehicle-derived $PM_{2.5}$ and/or traffic emissions noted in epidemiological or highway proximity studies, especially those examining effects prior to the mid-1990s. Toxicology studies are especially important for understanding the role of CO in causing adverse cardiopulmonary health effects for two reasons. First, because many components of vehicular emissions are highly correlated with each other, toxicology may help elucidate the potential role(s) of each in adverse health outcomes. Second, "area monitor" epidemiological studies, in hindsight, appear to have unforeseen handicaps in assessing CO associations. While several studies, including some "area monitor" studies, found positive associations between CO and cardiopulmonary effects (e.g., Mann et al., 2002; Herbert et al., 2000; Stern et al., 1988; Burnett et al., 1997, 1998), other area monitor studies did not (Pope et al., 1995, 2002). Often, associations with adverse cardiopulmonary outcomes are found more consistently with regionally widespread PM_{10} and $PM_{2.5}$ than with CO when both PM and CO are examined in the same study. Since CO levels can vary by a factor of 6 within only 200 m at different sites upwind and downwind of a major freeway (Zhu et al., 2002a, 2002b), it seems likely that variable monitor location might explain the less consistent results for CO among different studies.

Although there has been relatively little toxicological assessment of possible chronic cardiopulmonary effects of CO, one study (Thom et al., 1999) showed that rats exposed to 50 ppm CO for 1 h developed increased capillary permeability and enhanced low-density lipoprotein (LDL) oxidation. The authors suggested that due to oxidative stress, the results offered a biochemical mechanism that may explain an association between atherosclerosis and chronic CO exposure. The authors did not assess whether CO concentrations lower than 50 ppm might cause similar effects.

As late as the mid-1990s, commuters on major urban arterials typically were exposed to peak CO concentrations of 10–20 ppm (Ott et al., 1994). However, in the 1970s, CO levels inside cars were often over 100 ppm (Anderson et al., 1973). Potentially atherosclerotic effects in rodents (Thom et al., 1999), thus, occurred at exposure levels below those typical for some humans in the 1970s, and at an average multiple of only 5 times urban arterial highway CO concentrations in the mid-1990s. It is possible that a portion of adverse health effects associated with traffic PM might have been caused by long-term exposure to CO. In contrast, many toxicological studies of $PM_{2.5}$ or of its constituents, especially in vitro or instillation animal studies, evaluated health effects using concentrations thousands of times greater than their ambient levels.

Because some people with congestive heart failure (CHF) have difficulty getting adequate tissue oxygenation, moderate levels of CO could induce heart failure in those with advanced CHF. In a study of angina in human subjects (Anderson et al., 1973), exposure to 50 ppm CO (4 h/day, 5 consecutive days) increased carboxyhemoglobin levels from 1.3% to 2.9%, and reduced the mean duration of mild exercise before onset of pain. Electrocardiograms recorded during and after exercise showed worsening of ST-segment changes, with earlier onset and longer duration of ST-segment depression. The authors concluded that low levels of CO can cause worsening of myocardial ischemia in patients with angina pectoris.

The results just described were confirmed in a later and larger study (Allred et al., 1989, 1991) that demonstrated a dose-dependent, statistically significant decrease in the time to ST-segment changes and to onset of angina at higher levels of CO (117 and 253 ppm). The authors reported that mean carboxyhemoglobin levels in study subjects, after exposure to 100 ppm CO for 4 h, were less than those in subjects in another study who were exposed to traffic emissions for 90 min of heavy freeway travel at the time. Thus, significant acute health effects were found at levels similar to those many humans routinely experienced at the time of studies examining relationships between air pollution and health (Pope et al., 1995, 2002). Acute cardiopulmonary effects caused by CO might have been additive to the chronic effects just discussed.

Another study (Burnett et al., 1998) discussed the toxicology of CO in assessing a finding that CO was associated with a large majority of excess deaths in Toronto from 1980 to 1994. The authors suggested that CO could increase mortality risks by interfering with homeostasis via alterations in the NO-cGMP signaling pathway.

In summary, there have been several toxicological studies evaluating the effects of CO, involving both human and animal subjects, at exposure concentrations equivalent to those in ambient air at and near heavily trafficked roads that were noted in the 1970s and early 1980s, and less than an order of magnitude higher than such levels in the 1990s. These studies and findings reviewed in Burnett et al. (1998) suggest that CO could have played an important role in both chronic and acute mortality reported in previous epidemiological studies.

Other Vehicular-Derived Pollutants

The role of vehicular emissions that are highly associated with CO—such as ultrafine PM (UF), semivolatile organic compounds (SVOCs), diesel exhaust particles (DEP), black carbon, and various other carbonaceous components such as elemental carbon (EC) and organic carbon (OC)—should also be more fully explored, to understand the role they may play in premature mortality via cardiopulmonary effects. Because of the ubiquity of vehicular traffic, most ambient urban UFs that people breathe are likely to be from vehicles. Such vehicular-derived UFs are likely to consist of complex carbonaceous species, including condensed SVOCs, which increase in number in cooler temperatures.

In the last 3 yr, there have been many in vitro studies investigating the toxicity of such particles, especially DEP and UFs. Two of these (Hiura et al., 1999, 2000) showed that DEP induced apoptosis in pulmonary alveolar macrophages via production of reactive oxygen species (ROS). The researchers noted that carbon black (control particle) did not produce these effects, which they suggested were due to unburnt organics in the DEP.

Another study (Li et al., 2002a) showed that DEP caused oxidative stress, interleukin-8 (IL-8) production and cytotoxicity, in a dose-response manner in bronchial epithelial cells. Other research (Li et al., 2002b) demonstrated that organic DEP extracts induced oxidative stress in a dose-responsive manner in two lines of macrophages, leading ultimately to apoptosis, as in Hiura et al. (2000). This study also examined the effects on these cells of CAPs collected from nearby a major highway. The researchers found that the CAPs "mimic the effects of organic DEP extracts at lower oxidative stress levels," suggesting that the DEP component of CAPs were likely responsible for the oxidative stress. The oxidative effects were positively correlated to the higher organic carbon (OC) and polyaromatic hydrocarbon (PAH) content of fine PM versus coarse PM, as well as the rise in PAH content that occurs in coarse PM during the winter months. Additionally, the study found that while both fine and coarse CAPs were toxic, they were both considerably less potent than was DEP in inducing apoptosis, suggesting the possibility that the non-DEP portions of fine and coarse PM may be less toxic when considering this response.

Two recent in vitro studies extended the inquiry from DEP to submicrometer and ultrafine vehicular emissions. In one

(Li et al., 2003), the authors reported that ultrafine CAPs from the Los Angeles, CA, basin are more potent than were fine or coarse CAPs in inducing oxidative stress, including expression of heme oxygenase 1 (HO-1); fine particles also showed these effects, but to a lesser degree. Electron microscopy showed that UF particles penetrated into subcellular structures and damaged mitochondria. The HO-1 expression was directly correlated with the high organic carbon and PAH content of UF. These findings suggest that the results reported by Hiura et al. (1999, 2000) may have been due to the UF portion of DEP.

In a study (Huang et al., 2003) examining the cellular effects of $PM_{1.0}$, $PM_{1.0-2.5}$, and $PM_{2.5-10}$ collected with a trichotomous impactor in Taiwan, $PM_{1.0}$ resulted in significantly higher IL-8 production and lipid peroxidation than did $PM_{2.5-10}$, whereas the responses elicited by $PM_{1.0-2.5}$ were not significantly higher than blank filters (controls). The $PM_{1.0}$ also stimulated more tumor necrosis factor (TNF-α) production by pulmonary alveolar macrophages than did either of the larger particle size fractions. In examining the constituents of $PM_{1.0}$, the authors found that cytokine production was significantly associated with the metal content; IL-8 correlated with Cr and Mn, and TNF-α with Fe and Cr. Lipid peroxidation in bronchial epithelial cells correlated with both elemental and organic carbon content. Effects on these biological endpoints showed no correlation with sulfate concentration.

This study, conducted in a country with a somewhat different mix of PM components than in the United States, appears to generally confirm the findings of Li et al. (2003) that the smaller particles are the most toxic, that markers of oxidative stress are present, and that organic and elemental carbon are important. The possible role of metals in these responses was not examined in Li et al. (2003), so the findings with regard to metals reported by Huang et al. (2003) neither support nor contradict those of Li et al. (2003).

While results of in vitro studies do not necessarily predict what will happen when humans are exposed to ambient pollution, the findings of the studies just described suggest that, at least for some health endpoints, specific components of the UF fraction of vehicular PM emissions may be quite toxic, while others might be less so. In general, however, not enough is yet known about the relative toxicity of constituents of vehicular emissions and/or roadside fine PM dusts. Furthermore, it is not as yet known whether fine PM mass in close proximity to major roads is particularly harmful, or whether carbonaceous material, CO, semivolatile organics, ultrafine PM, and/or specific components of ultrafine PM from vehicles are most dangerous, since these emissions all strongly covary.

THE ROLE OF SECONDARY SULFATES IN ADVERSE HEALTH EFFECTS: STUDIES REEXAMINING CENTRAL-MONITOR STUDIES

Sulfate is the largest single component of $PM_{2.5}$ in the eastern United States and is therefore highly correlated with $PM_{2.5}$. Thus, any health associations with sulfate are difficult to separate from those of $PM_{2.5}$ in general. In this section, we review three area monitor analyses that explicitly attempted to determine whether sulfates and/or acidity were the component(s) of PM most likely to be causally linked with human health effects.

Dockery et al. (1992) compared the strength of health associations among PM_{10}, $PM_{2.5}$, SO_4, and H^+, in St. Louis, MO, and in Harriman, TN. This study tested the hypothesis that the strength of association would become stronger as particle size decreased and acidity increased, e.g., that the association with daily mortality would increase from PM_{10} to $PM_{2.5}$ to SO_4 to H^+. The authors reported the opposite, however. In St. Louis, the only significant association was with PM_{10}; $PM_{2.5}$ was close to significant, sulfate was far from significant, and H^+ was farther still. There were no significant findings in Harriman, a much smaller location, although the overall pattern was similar.

Schwartz et al. (1996) reexamined the data from Dockery et al. (1993) and found that PM_{10}, $PM_{2.5}$, and SO_4 were all associated with increased daily mortality, but that acidity was not. Further analysis led the authors to state. "These associations are not attributable to the sulfate or acidic composition of these particles."

Lippmann et al. (2000) again adopted the hypothesis that strength of association would increase with smaller particle size, with SO_4 and H^+ having stronger associations than TSP, PM_{10}, and $PM_{2.5}$. Again, as in Dockery et al. (1992), the researchers found the opposite: "In general, the PM mass indices were associated more significantly with health outcomes than were H^+ and SO_4."

Consistent with the epidemiology just described and in contrast to studies of various vehicular emissions, a recent review of the toxicology of the largest fraction of regional $PM_{2.5}$ in many areas, for example, secondary sulfates and nitrates, found that ambient levels appeared to have little toxicity (Schlesinger & Cassee, 2003). The authors state that "evaluation of the toxicological database suggests that these particles have little biological potency in normal humans and animals, or in the limited compromised animal models studied at environmentally relevant levels," while recognizing several caveats that required additional investigation.

Because the great majority of studies that have found associations between sulfates and human health are area monitor studies, we believe the findings of the few studies that attempt, using data from such studies, to parse out the effects of sulfates and acidity from those of PM mass indices are important, particularly in the context of the other types of studies reviewed herein.

"MODERN" AREA MONITOR STUDIES

As previously noted, the great majority of "area monitor" studies are unlikely to be able to pinpoint specific types of PM, gases, or sources that might be associated with adverse health effects, partly because they implicitly assume that all

people in a study area are exposed to the same concentrations of pollutants, and partly because most of these studies measured only one or two PM mass metrics, generally sulfate and sometimes nitrate, and up to four gases (NO_2, CO, SO_2, and ozone). We now know that levels of several pollutants are far higher within 150 m of major roads, sometimes an order of magnitude higher (Zhu et al., 2002a, 2002b), and that adverse health effects are associated with living in such close proximity (Hoek et al., 2002; Lin et al., 2002; Venn et al., 2001). Levels of pollutants are also higher near major industrial emitters (Jerrett et al., 2001). Area monitor studies that improve upon the early basic design of such studies may provide more precise findings.

Ebelt et al. (2005) developed separate estimates of exposures to ambient and nonambient PM of different size ranges, as well as to sulfate and nonsulfate ambient exposures and concentrations, in Vancouver, Canada, combining monitoring and personal exposure data. Using mixed effects models in a small panel study (16 subjects with COPD), the authors calculated that $PM_{2.5}$ nonsulfate ambient exposures and/or concentrations were significantly associated with several important health endpoints, including reduction in systolic blood pressure, superventricular ectopy (SVE) response (an arrhythmia variable), and reduction in heart-rate variability (r-MSSD). Another measure of heart-rate variability, reduction in SDNN, was barely insignificant. None of the $PM_{2.5}$ sulfate concentrations or exposures were significant for these endpoints. Because of the small number of subjects and low sulfate levels, the authors view their findings as preliminary and also suggest that the study be repeated in areas where secondary sulfate levels are higher.

The Aerosol Research and Inhalation Epidemiological Study (ARIES) is the first epidemiological study to measure a large number of air quality variables, thereby enabling possible associations with many more pollutants to be explored. ARIES measures several gases and many PM components, including total metals, water-soluble metals, OC and EC, sulfates, nitrates, several speciated hydrocarbons, and polar volatile organic compounds (VOCs). ARIES examines the relationship between air quality and five different health outcomes: daily mortality, emergency room (ER) visits, heart-rate variability (HRV), arrhythmic events, and unscheduled physician visits. Results of 1 yr of ARIES air quality and health data (Tolbert et al., 2000) found significant, positive associations generally for vehicle-related emissions: dysrhythmia with CO, coarse PM, and $PM_{2.5}$ EC, and all cardiovascular diseases with CO, $PM_{2.5}$ EC and $PM_{2.5}$ organic matter. No associations with health outcomes were found with sulfates or nitrates.

A recent follow-up study, with added years of data (Metzger et al., 2004), found associations for cardiovascular emergency room visits with NO_2, CO, $PM_{2.5}$, OC, EC, and oxygenated hydrocarbons. Taken as a whole, these would also be viewed as generally vehicular emissions. No associations were found with sulfates, nitrates, or soluble metals.

A source apportionment study (Janssen et al., 2002) explored how the prevalence of central air conditioning might change the association of outdoor PM exposure with health effects in hotter regions of the United States and thus might enable a more accurate measure of such associations. With central air conditioning, air exchanges with outdoor air are usually minimized, thus reducing exposure to ambient pollutants. With effect modification due to use of central air conditioning systems now taken into account, the authors reported that hospital admissions for cardiovascular disease increased significantly with increased concentrations of PM_{10} derived from highway vehicles and diesels and from oil combustion, but not from coal combustion. The authors also examined vehicle miles traveled per square mile (VMT) as a variable. VMT was highly correlated with the highway emission variables, and also yielded a significant positive association with hospital admissions for cardiovascular disease. Thus, the findings of Janssen et al. (2002) are corroborative of the results just described that suggest the importance of emissions from transportation sources, as well as from another local source with a significant presence in only a few cities, namely, residual oil.

REINTERPRETATION OF TWO PIVOTAL COHORT STUDIES

Two area monitor cohort studies, the American Cancer Society (ACS) study (Pope et al., 1995, 2002) and the Six Cities study (Dockery et al., 1993), are among the studies most cited as evidence that both $PM_{2.5}$ and sulfate are associated with premature mortality. In each study, $PM_{2.5}$ and sulfate are highly correlated. Thus, as previously noted, health associations with $PM_{2.5}$ are likely to also occur with sulfate, if only due to this correlation. Is there internal evidence in these studies suggesting that health impacts caused specifically by secondary sulfates might actually be weak?

In the ACS follow-up study (Pope et al., 2002), a significant, positive association between increases in annual $PM_{2.5}$ concentrations and mortality endpoints (cardiopulmonary, lung cancer, and all-cause) were found only for those people with a high school education or less. For those with better than a high school education, the relative risks of mortality for cardiopulmonary, lung cancer, and all-cause mortality were virtually zero. Since regional masses of $PM_{2.5}$, including secondary sulfate levels representing about one-third or more of the $PM_{2.5}$, are widespread in the East, those with better than a high school education are exposed to secondary sulfate, but apparently without any adverse health impact. Thus, it seems implausible that secondary sulfate would be the cause of adverse health impacts associated with $PM_{2.5}$, since a large group of people appears to be unaffected by secondary sulfate and other components of regional air masses.

Why is it, then, that only those people with low socioeconomic status (SES) might be adversely affected by $PM_{2.5}$ levels? People with lower SES are exposed to almost an order of magnitude more traffic near their homes (Reynolds et al.,

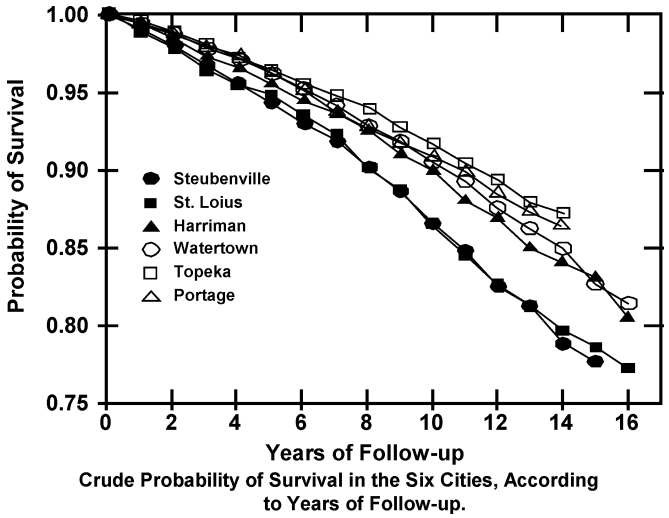

FIG. 1. Crude probability of survival in the Six Cities. From Dockery et al. (2003).

2001), and live closer to large industrial sites and are exposed to more industrial air pollution (Jerrett et al., 2001).* Coke oven emissions are highly carcinogenic (U.S. Department of Health and Human Services, 2002), and there is concern that diesel emissions may also cause lung cancer (U.S. EPA, 2002). As already reviewed, vehicular (Hoek et al., 2002; Mann et al., 2002; Janssen et al., 2002; Lin et al., 2002) and industrial emissions (Somers et al., 2004) are strongly associated with adverse health effects. Krewski et al. (2000) report that those with less than a high school education are exposed to significantly more occupational dirtiness and occupational lung carcinogens than those with greater than a high school education in the ACS study. Thus, those with lower SES are exposed to more dangerous types of air pollution than secondary sulfate, and it seems likely that these exposures drive the overall results of Pope et al. (2002), explaining the absence of any health effects for those with better than a high school education.

The "Six Cities" study examined the relationship of $PM_{2.5}$ and sulfate concentrations with premature mortality in several small cities (Portage, WI, near Madison; Topeka, KS; Harriman, TN, near Knoxville; and Steubenville, OH) and two large ones (St. Louis, MO, and Boston) from 1978 through 1988. In comparing the most polluted city for $PM_{2.5}$ (Steubenville) with the least polluted one (Portage), the authors found elevated risks for both all-cause mortality and cardiopulmonary mortality in the former. They also found that the crude probability of survival over 16 yr among the six cities was sharply lower only in Steubenville and St. Louis (see Figure 1). After examining data on the different types of emissions in the different localities, we conclude that the Six Cities study appears to be a good illustration of differential effects of different emission types.

In Steubenville proper, there was an assortment of blast furnaces, open hearth furnaces, and other hot and cold metal-working facilities at the time of the study. About 3 miles downriver, there were over 600 acres of coking facilities, capable of making about 5000 tons of coke per day.* In addition to these facilities, additional steel-making facilities were about 3 miles upriver in Weirton. Given the toxicity of precontrol coke oven emissions, and perhaps of concentrated steel making as well, it isn't surprising that Steubenville pollution was more toxic than that in most of the other cities examined.

Both sulfate and $PM_{2.5}$ levels were sharply higher in Steubenville than in St. Louis. If sulfate and $PM_{2.5}$ mass were the important causal agents, we would expect survival rates over time in Steubenville to be far lower than in St. Louis, yet the rates were virtually the same. We suggest that the reason the mortality rates were virtually the same in these two cities, and sharply higher than in the other four is that in the 1980 time frame, both cities were highly industrialized with older industries, setting them apart from the others.

St. Louis, too, had a mixture of pollution sources with high toxicity that was atypical for most of the U.S. These included a large coke facility (Carondelet Coke, now defunct), various local industrial facilities including steel making, and a lead smelter and more steel making 4 miles north in Granite City, IL. The relative toxicity of industrial emissions in St. Louis is suggested by a comparison of $PM_{2.5}$ and sulfate levels in Harriman/Knoxville with those in St. Louis. Harriman and St. Louis had identical sulfate measurements (8.1 $\mu g/m^3$), and similar total $PM_{2.5}$ concentrations (20.8 vs. 19.0 $\mu g/m^3$, respectively). A 1700-MW TVA coal-fired power plant was in close proximity to the monitor location in Harriman. If secondary sulfate or $PM_{2.5}$ mass were the major source of health effects, we would expect to see similar mortality rates in the two areas. Yet people in St. Louis had a far lower probability of survival than those in the Harriman area (see Figure 1). We suggest it is the nature of the type of industrial emissions in St. Louis, as well as higher vehicular emissions in the larger city, that is related to the sharply lower probability of survival there in comparison to Harriman. (Different SES status, here defined as poverty rate, is unlikely to explain the differences in survival rates between Steubenville, St. Louis, and Harriman, because the poverty rates for these localities in 1979—14.3%, 21.8%, and 19.6%, respectively†—show Steubenville lower than St. Louis, and St. Louis and Harriman/Knoxville very similar [U.S. Bureau of the Census, 1988].)

Krewski et al. (2000) examined exposure by educational level to a known or suspected occupational lung carcinogens

*Low SES in Reynolds et al. (2001) refers to lower family income; in Jerrett et al. (2001) low SES refers to lower income, increased unemployment, and lower value of dwellings. Unemployment and lower income levels are highly correlated with lower education levels.

*See http://wheeling.weirton.lib.wv.us/history/bus/whsteel1.htm and http://es.epa.gov/oeca/main/strategy/rjo/98/rjo-182.html for fuller description of Steubenville facilities.

†Knoxville data used for Harriman data, which were not available.

for both the ACS and six cities studied: 5.52% of those with less than a high school education, 3.68% of those with just a high school education, and 1.61% of those with more than a high school education were found to be exposed to such lung carcinogens (Krewski et al., 2000, Table B-11, Appendix B). Thus, occupational exposure to carcinogens is another likely possibility for explaining why those with low SES have significant associations between PM and lung cancer, but those with higher SES do not (in Pope et al., 2002), for why people in St. Louis and in Steubenville have similarly low survival rates despite sharply different sulfate and $PM_{2.5}$ concentrations (Dockery et al., 1993), and for why people in St. Louis and Harriman have very different survival rates despite identical sulfate levels and nearly identical $PM_{2.5}$ levels.

We conclude from this evaluation of the Six Cities study that local emissions of the type found in the late 1970s and early 1980s in some industrial Midwestern cities appeared to be more toxic than some other types of PM, and that this toxicity, not sulfate or $PM_{2.5}$ mass concentrations, is a more likely cause for health impacts in this small group of cities.

TOXICITY OF PRIMARY METAL SULFATES VERSUS SECONDARY SULFATES

Use of the term "sulfate" can unwittingly create confusion, if primary metal sulfates—important constituents of some fly ashes, such as those from residual oil, and also emitted from other local sources, such as smelters—have toxicity not found with secondary sulfates. Effects associated with primary metal sulfates should not be attributed to "sulfates" in general, if secondary sulfates have minor or negligible health effects.

Laden et al. (2000) examined daily mortality in the same six cities as Dockery et al. (1993), but utilized trace-element emissions and factor analysis to try to isolate sources of harmful emissions. When combining data from all six cities, the authors found significant associations between daily mortality and emissions in 1979–1988 from vehicles, using lead (Pb) as a tracer element, and from coal emissions, using selenium (Se) as a tracer. This study also found that sulfur (S, measured as sulfate) was significantly associated with daily mortality in the combined analysis. For both Se and S, Boston was the lone city with a significant association. The coefficients of effect in Boston were much higher than in cities with greater S and Se levels, in some cases by more than an order of magnitude.

These results are puzzling, because Boston had the lowest Se levels, and the fourth lowest S levels, of the six cities. Highway proximity studies of mortality and morbidity usually show a dose-response function—those living closest to the road have the largest adverse health effects (Lin et al., 2002; Hoek et al., 2002). However, in Laden et al. (2000), there appears to be a *reverse* dose-response function. Why would the city with the lowest ambient concentration of the tracer for coal (Se) have a much higher coefficient for mortality risks for the coal factor, and be the only city where this figure is significant? A similar question can be raised for the S factor.

A new analysis (Grahame & Hidy, 2004) suggests an explanation. Using three different methods and a U.S. EPA database for trace elements of residual oil emissions, the authors suggested that over half the very small amount of selenium found in Boston air in Laden et al. (2000)—0.7 ng/m^3—came from the 1700-MW residual oil plants 5 to 6 miles from the Boston-area monitor and from other local residual oil burning, and about half the sulfate wasn't secondary sulfate but rather was primary vanadium and nickel sulfate from nearby residual oil sources. The authors cite Schlesinger and Cassee (2003) as evidence that secondary sulfates and nitrates are unlikely to cause mortality at ambient levels, and Costa and Dreher (1997) to show that residual oil fly ash (ROFA), with its primary vanadium and nickel sulfate emissions, is likely to be more toxic than emissions from coal units. These results suggest that local primary emissions from residual oil, at the higher levels prevailing in the 1970s and early 1980s, may have had important local health impacts near the limited number of localities in which the oil was extensively used.

Grahame and Hidy (2004) also hypothesized that because only one monitor was used in Boston in Laden et al. (2000), and because this monitor was about a mile north of a heavily used interstate highway, there is a possibility that on days with stagnant airflow conditions when both pollution and mortality were higher the monitor might not pick up much of the increase in traffic emissions due to the distance from the highway (since highway pollutants drop back to near-normal levels within 300 m; Zhu et al., 2002a, 2002b), but might instead pick up an increase in residual oil emissions. If this were the case, then perhaps vehicular emissions would have more association with mortality, and coal or residual oil emissions less so, in Boston in 1979–1988.

With this reinterpretation of Laden et al. (2000), the results are now consistent with those of Janssen et al. (2002), such that only vehicular and residual oil emissions are statistically associated with adverse health outcomes.

SUGGESTIONS FOR FURTHER RESEARCH

Some chemical reaction pathways involving sulfates may be involved in the production of PM species that may indeed be harmful to public health even if secondary sulfates per se may not be. Such pathways include:

1. Acid catalysis of organics.
2. Sulfate aerosol as condensation nucleus.
3. Enhancement of bioavailability of metals by combination with secondary sulfates.

Laboratory experiments suggest that when sulfuric acid (H_2SO_4) is formed in the atmosphere from SO_2 oxidation, prior to neutralization by ammonium, the acid catalyzes reactions of atmospheric volatile organic species to larger organic species, thus increasing PM mass (Jang et al., 2002). Work is needed to understand the potential toxicity of such particles (i.e., precursors vs. catalyzed products) and to understand the extent

to which such particles are produced by acid catalysis in the actual atmosphere. Some of the studies cited earlier found negligible toxicity from rural PM (Somers et al., 2004; Creason et al., 2001; Gent et al., 2003), suggesting that secondary organic aerosols produced by acid catalysis may have negligible toxicity; however, this issue needs to be examined in greater depth.

A new factor analysis (Lee et al., 2003) found that the secondary coal factor, high in secondary sulfate and nitrate as well as selenium, has surprising little (secondary) organic aerosol associated with it. Instead, another factor—organic acids, which is low in sulfate, nitrate, and selenium—was high in secondary organic aerosols. This factor appears to have different sources than the factor that would produce acid catalysis, but its constituents might still undergo acid catalysis to an unknown degree.

Secondary sulfates may present good condensation nuclei for small (UF) particles. It would appear than at least two questions are paramount here: (1) To what extent are secondary sulfates necessary for nucleation (e.g., would there be appreciably less nucleation of tiny particles in urban air in the absence of secondary sulfates)? (2) Would UF particles be more harmful to health, or less harmful, in the absence of secondary sulfate condensation nuclei?

Another issue is to what extent metals are made more bioavailable by secondary sulfates. This issue breaks down to two related questions: (1) To what extent are ambient levels of $PM_{2.5}$ metals a local health problem, or a widespread one? (2) To what extent are nonsoluble ambient $PM_{2.5}$ metals made soluble by contact with secondary sulfates? A natural "intervention" study that occurred when a steel plant in Utah was shut down for a year strongly suggests that the reduction in metal content of the $PM_{2.5}$ was responsible for the drop in respiratory hospital admissions during the closure (Frampton et al., 1999). An increased inflammatory response was found when PM from the years the steel mill was operational was instilled into the lungs of human volunteers, compared to PM from the year it was closed (Ghio & Devlin, 2001). Both studies found elevated levels of a potent cytokine (IL-8) in the year before and the year after the plant was closed. However, a CAPs exposure study in Chapel Hill, NC, using human volunteers found no elevation in IL-8, suggesting the absence of enough metals to cause inflammation from this type of $PM_{2.5}$, even in concentrated form (Ghio et al., 2000).

The extent to which secondary sulfates interact with ambient metals to make the latter soluble is unclear. An examination of 1981 and 1982 metal PM from North Provo, UT, near the steel mill, before its 1-yr closure found that the water soluble and insoluble fractions were 13.1% and 86.9% of the total mass (Ghio et al., 1998). Both the water-soluble and insoluble fractions increased release of IL-8 in rodents, compared to saline control. The authors concluded that the ambient particles included concentrations of ionizable metals in both fractions. Two tentative conclusions may be drawn from this study: (1) While metals induce more IL-8 production on an equal mass per unit of soluble metal basis (based on installation at high doses) compared to insoluble metal, both forms of metals are potentially harmful; and (2) it isn't clear how easily secondary sulfates can solubilize metals in ambient air, given the higher amount of metals in the insoluble fraction and considering that emissions from a steel mill likely include some primary metal sulfates. Further study is needed to understand the extent to which reducing secondary sulfates would make ambient metals less soluble.

Further studies, using increasingly precise tools, may demonstrate links between a by-product of secondary sulfate formation and a specific health effect. Whether this eventuality occurs or not, it is crucial for public health to understand which components of air pollution are more harmful and which are less harmful. The NRC (2004) recently made several highly relevant research proposals, specifically recommending research that uses the *same* experimental protocol related to a particular health outcomes, and the *same* multiples of ambient PM levels of different types of PM, in studying several different pollutants or sources to directly compare the exposure-dose-response relationships (i.e., relative toxicity and no-effects levels) of different types of particles. Use of this protocol will enable a better understanding of the relative toxicity of different emission sources and PM types.

CONCLUSIONS

The totality of the evidence presented in this article suggests the following conclusions:

1. In contrast to "standard" area monitor studies, which normally use few PM variables, studies that can determine whether a harmful air mass was urban or rural (Somers et al., 2004; Creason et al., 2001; Gent et al., 2003) or that can pinpoint the sources from which emissions derive or otherwise "tease out" separate effects of secondary sulfates from other types of PM (Godleski et al., 2000; Tolbert et al., 2000; Janssen et al., 2002; Wellenius et al., 2003; Metzger et al., 2004; Grahame & Hidy, 2004; Ebelt et al., 2005) generally found that secondary sulfates, rural air masses, or emissions from coal-fired power plants were not associated with adverse health effects, but that vehicular, industrial, and/or residual oil emissions or urban masses were so associated.
2. Toxicology studies have identified mechanisms by which specific components of vehicular, industrial, or urban emissions might be harmful, but find that secondary sulfates and nitrates appear not to be harmful at ambient concentrations (reviewed in Schlesinger & Cassee, 2003).
3. Numerous "emission gradient" studies have found adverse health effects, including cardiopulmonary mortality and morbidity as well as respiratory effects, associated with exposures at short distances from major local emission sources, such as major roads, which are concentrated in urban areas.
4. Reanalyses using area monitor data that specifically examined whether sulfate or acidity were more likely than

PM mass measures to be strongly associated with health effects found that sulfate and acidity were less likely to be so associated.

5. For the two major U.S. area monitor cohort studies that found associations between premature mortality and both $PM_{2.5}$ mass and sulfate (Dockery et al., 1993: Pope et al., 1995, 2002), there appear to be more compelling alternative explanations for the adverse health effects, namely, vehicular and industrial emissions.

Thus, other than "standard" area monitor studies that usually find health associations for PM masses and types with the least local variability, the available database suggests that secondary sulfates and rural air masses in eastern North American appear to cause negligible adverse health effects. Despite many area monitoring studies associating PM, and often specifically sulfate as well, with adverse health outcomes, it appears that recent epidemiological and toxicological studies that are better able to distinguish among sources of PM, chemical constituents of PM, and types of air masses generally have found that it is vehicular and industrial emissions and urban air masses that are toxic, rather than rural air masses or secondary sulfates. These findings are supportive of the numerous comments in the literature that different types of PM are likely to have different toxicities, and that it is important to determine which particles are primarily responsible for adverse health effects in order to best protect the public health (CASAC, 1996; National Research Council, 1998; Ware, 2000; Mittleman & Verrier, 2003; National Research Council, 2004). Additional research should be undertaken to further understand the toxicity of particular sources and types of PM, including further work on secondary sulfates.

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