



**Department of Energy**  
Washington, D.C. 20585  
March 30, 2005

U.S. Environmental Protection Agency  
Attention: Docket ID No. OAR-2001-0017  
(by email to [a-and-r-Docket@epa.gov](mailto:a-and-r-Docket@epa.gov))

Dear Sir:

The Department of Energy has reviewed the "Second Draft Staff Paper for Particulate Matter," (Draft Staff Paper) as distributed with notice at 70FR5442, February 2, 2005. We wish to offer the following summary comments, and the enclosed detailed comments, to assist EPA in formulating its final Staff Paper, and in developing possible revisions to EPA's Ambient Air Quality Standards for Particulate Matter. Our comments, concerning studies of human health effects performed since April 2002, suggest that EPA take these studies into account before reaching conclusions on the health consequences of particulate matter and, more significantly, specific types of particulate matter, before developing possible revisions to EPA's Ambient Air Quality Standards for Particulate Matter.

The Draft Staff Paper appropriately focuses on scientific information developed since 1997, the end of the last review cycle for the ambient standard. The Draft Staff Paper is properly focused on the types of issues it should consider. However, we are concerned that a large body of information that has become available since April 2002 has not been considered in the Staff Paper, and may not be adequately considered in possible revisions to the ambient standards later this year.

These more recently published refereed articles use newer or more comprehensive approaches than the more dated studies on which EPA Staff appear to place primary emphasis during this review. Taken together, they offer insight into which types of particulate matter may be the most damaging, and which types may provide relatively little or no harm to public health. These studies appear to us to be exactly the type of research and analysis recommended to EPA in earlier recommendations by the National Research Council. Full citations and general findings of these studies are included in the attached detailed comments.

Questions regarding these comments should be referred to Thomas Grahame, at 202-586-7149.

Sincerely,

David Conover  
Principal Deputy Assistant Secretary  
Office of Policy and International Affairs

Enclosure: Comments of U.S. Department of Energy on EPA Second Draft Staff Paper for Particulate Matter

## **Comments of U.S. Department of Energy on EPA Staff Paper for Particulate Matter**

March 30, 2005

### **Summary**

These comments relate only to the aspects of the January 2005 draft EPA Staff Paper that address health effects associated with PM<sub>2.5</sub> (i.e., the primary National Ambient Air Quality Standards). The Draft Staff Paper presents a generally comprehensive overview of refereed epidemiological and toxicological studies published prior to April 2002. The Staff Paper emphasizes the findings of the “Six Cities Study” (1993), and the American Cancer Society Studies (1995, 2002). The Draft Staff Paper recommends maintaining the current form of the standard (all particles smaller than 2.5 microns diameter, an annual average standard, and a 24-hour average standard), and appears to recommend a general lowering of the standard. These findings could have substantial impacts on air quality management programs in the U.S., including calls for revisions of State Implementation Plans, requirements for permitting new facilities that emit particulate matter, and the general focus of future regulation of air pollutants.

Our greatest concern with the draft Staff Paper is that it fails to consider a broad body of additional, refereed, epidemiological and toxicological literature published after April 2002. Many of these more than two dozen studies use newer techniques to overcome methodological shortcomings of previous work in this field. In our view, these studies are highly responsive to criticisms, such as those offered by the National Research Council, that health assessments of PM should differentiate between the types of particles (and indeed the categories of emission sources) that are most relevant to health effects from particulate matter, versus those particles that likely contribute very little or none to health effects. These studies cluster into four groups:

- Epidemiological studies using a new “gradient” approach to assess different health effects resulting from different exposure levels of air pollutants from a particular source;
- Toxicological studies using a relatively new approach that concentrates air pollutants, to allow consideration of specific subcategories of fine particles;
- Epidemiological studies that consider a larger suite of possible air pollutant species causing adverse health effects, than did studies prior to April 2002; and
- Studies using new statistical techniques and more thoughtful analysis of source category surrogates than earlier studies, to separate the effects of primary metal sulfates from secondary sulfates.

Our interpretation of these newer studies is that they point in the direction of additional controls for certain species of fine particles, such as carbonaceous particles and metallic sulfates associated with oil combustion, and away from a more stringent standard based on undifferentiated fine particles, and certain species of fine particles.

It is understood that Section 109(d) of the Clean Air Act provides for a review of the criteria document every five years, and that it is administratively convenient to postpone review of this newer data until the next review cycle. Nevertheless, we believe that sound public policy dictates that EPA not ignore studies published over the past three years when conducting a review that, by definition, focuses on the scientific information generated since the previous review of the standards (1997).

## **Introduction**

The Draft Staff Paper reflects the state of the science regarding the health effects of PM as it existed in April 2002. This was the cutoff date for papers to be considered in the Criteria Document (CD, the required assessment of scientific findings with regard to particulate matter). If the state of PM health effects science remained substantially the same after April 2002, the absence of the most recent three years of science from consideration might not matter a great deal. However, the state of PM health effects science has undergone a transformation in the last three years.

This transformation includes the following elements:

1. Several replications of a new type of epidemiological study which relates differences in *actual* exposure within an area of study, to different mortality risks; and
2. Toxicological studies demonstrating that the chemical composition of the particle matters as much as or more than the particle size, and demonstrating that particular chemicals appear to be dangerous, while others appear not to be, within the same size fraction of PM.

In addition, two other types of more sophisticated studies, while not new in 2002, were not as widely published before 2002 than afterwards; these studies provide corroboration for the first two elements above. These types of studies are:

1. Concentrated Ambient Particulates (CAPs) studies; and
2. Newer types of epidemiology studies which include more than the "standard" small suite of pollutants measured.

Finally, new studies post 2002 allow researchers to distinguish health risks of two different types of sulfates, secondary sulfates (formed by oxidation of SO<sub>2</sub> emissions from various sources in the atmosphere) and primary metallic sulfates, emitted directly from sources such as residual oil combustion in that form.

Many of these studies enable a direct comparison of the effects of different types of ambient particles, or of different sources of such particles, on the same health endpoints, thus allowing observers to distinguish which are more harmful, and which may not be harmful.

Taken together, these studies show -- as suggested by the National Academy of Science panel (the National Research Council) which has reviewed EPA's research plans for the past 7 years --

that certain sources or components of fine PM are the most problematic for health, but other components of the same size fraction may have little health impact. Depending on what sources of PM are regulated, and on what specific fractions of PM are regulated, public health benefits may vary significantly.

### **Associating Differences in Actual Exposure with Different Mortality Risks**

Virtually all epidemiology studies prior to April 2002 used data from one or a few central monitors, and assigned measured pollution levels to everyone living in the study area. In contrast, post April 2002, a number of studies have been undertaken which utilize known differences in pollution exposure within a study area, and find large differences in risks of mortality associated with these exposure differences, which can be large within distances of only a few hundred meters. For example, Zhu et al (2002a, 2002b) show that concentrations of several pollutants, such as black carbon, carbon monoxide, and ultrafines, can fall by a factor of 10 or more from a major Los Angeles freeway to a distance 150 yards away. Because these studies recognized that differences in distance from these major sources relate to differences in actual exposures, and related mortality risks to these differentials in distance and exposure, the interpretation of their meaning is far clearer than for the previous studies which assumed everyone was exposed to the same amounts of pollution measured, even though that was clearly not the case. These newer studies can be referred to as exposure gradient studies. Most are epidemiological, but some are toxicological (covered in the next section).

Epidemiological studies demonstrating relative risks of different exposures to the same source of pollution include the following.

- Hoek et al (2002) found that people aged 55 years and older and living within 100 meters of a major highway or within 50 meters of a major urban road had almost double the risk of cardiopulmonary mortality (1.95 relative risk) than did those living further from roadways. For all-cause mortality, the relative risk was 1.53 when the association was derived for those living at their initial address for 10 years or longer. These results suggest 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).
- Finkelstein et al (2004) found that people living close to a major road in Toronto also had an increased risk of mortality; the authors calculated that life expectancy was reduced for those living near a major road by 2.5 years, a diminishment similar to that of major diseases such as chronic pulmonary disease (3.4 years reduction) and chronic ischemic heart disease (3.1 years).
- Peters et al (2004) found a strong association between exposure to traffic and an MI (myocardial infarction, e.g., heart attack) one hour afterward. The time subjects spent in cars, on public transportation (non-subway), or on bicycles in traffic were all consistently linked with increased risk of MI. Here the exposure gradient is first, being in traffic, and secondly, length of time in traffic.

- Kuenzli et al (2005), in a study of the effects of air pollution in Los Angeles, where the great majority of pollution is from vehicles and where local electricity generation is now provided almost exclusively by natural gas, utilized a geostatistical model to assign fine PM levels to people living in different parts of the city. The authors found an increase in a subclinical measure of atherosclerosis in the carotid artery was significantly associated with increases in fine PM levels.
- In another study of the effects of air pollution on cardiopulmonary health in Los Angeles, Mann et al (2002) used an interpolation method to determine exposure of people to different pollutants; this method will determine individual exposure better than “central monitor” studies, which attribute the same level of pollution to everyone in a study area, but is perhaps less precise than the geostatistical model of Kuenzli et al. Mann et al found a 1 ppm increase in estimated 8-hour 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 also found an association with NO<sub>2</sub> concentrations, but 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.

These studies shed light on two earlier studies of heart disease, which previously have not received adequate attention, in bridge and tunnel workers in New York City, where the exposure gradient in one case was time of exposure rather than different levels of exposure. Stern et al. (1988) reported a significantly elevated risk of death from arteriosclerotic heart disease among tunnel officers as compared with bridge officers; exposures to 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 years 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.

The relevance of these *exposure gradient* studies to studies of particulate matter is twofold. First, vehicles mainly emit carbonaceous particles (as opposed to particles like secondary (ammonium and bi-ammonium) sulfates, which tend to be widespread over the eastern U.S.), and according to an EPA study (Rao et al, 2002), most of the increase in particles in urban areas is of carbonaceous particles. The second largest component of this “urban increment” is nitrate, which also mostly stems from vehicular emissions of NO<sub>x</sub>. Thus, in studies comparing mortality rates among different metropolitan areas, which find that larger cities tend to have larger pollution levels and higher risks of mortality than smaller localities, the great majority of “urban excess” PM in the larger areas (e.g., the amount of PM from the urban area, which when added to the regional PM becomes the total PM for the urban area) tend to be vehicular in origin. The exceptions would be localities with major industrial emitters, such as Steubenville, Ohio, a small locality with major emissions which can also be quite toxic (see next section). Secondly, these studies do not make it clear which specific emissions from vehicles are most responsible for the increased risk of mortality. Toxicology is necessary to make this determination.

In summary, then, because vehicular emissions carry with them a higher risk of mortality for those living near major highways, and because carbonaceous and nitrate fine PM from vehicles are the major reason PM is higher in larger cities with higher risk of mortality, associations in “central monitor” cohort studies of higher PM levels with higher mortality may be largely attributable to vehicular emissions.

## **Toxicology Studies**

The National Research Council Committee on Research Priorities for Airborne Particulate Matter (NRC, 2004) stated, “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...”

Toxicology studies, mostly new, suggest different components of vehicular and industrial emissions may be harmful, but that other types of emissions may not be. Regarding vehicular emissions, we will note toxicology on CO, and discuss at greater length toxicology of PAHs and semi-volatile vehicular emissions at greater length.

CO levels 3 decades ago were as high as 100 ppm on and near highways, but today are 20 to 40 times lower. Thus CO may have relevance for health effect associations (including mortality) in some epidemiological studies, e.g., at the far higher levels in the past, CO may have been responsible for some of the mortality risks found in time series and cohort studies in which increased risks of mortality were observed for periods from the late 1970s through the mid-to-late 1980s. Studies suggesting increased risks for those with ischemic heart disease, due to exposure to CO at ambient historical levels, are discussed in Grahame and Schlesinger (2005). It may also be possible that CO levels even today may have chronic effects for atherosclerosis – Thom, et al, 1999 found that a one hour exposure to 50 ppm CO in a rodent model caused increased oxidation of LDL cholesterol, raising the possibility that long term exposure to today’s CO levels could theoretically contribute to atherosclerosis.

PAHs (polycyclic aromatic hydrocarbons) are a known human carcinogen (U.S. Department of Health and Human Services, 2002) and are emitted from coke ovens, steel mills, and to a lesser extent in terms of concentration but a greater extent geographically by vehicles. The carcinogenicity of PAHs is further confirmed by a new study by McDonald, et al (2004), who stated that “The specific nitro-PAHS important for mutagenicity were the same chemicals that have been implicated by decades of bioassay-directed fractionation.”

In a series of articles, Li et al (2002a, 2002b, 2003) show that organic particles in emissions from diesel exhaust (DEP) cause oxidative stress in lung cells; that ambient fine PM from Los Angeles causes the same oxidative stress; that the stress was greater when the emissions were freshest but remained in aged fine PM; that coarse PM from Los Angeles can cause these effects, in winter and fall only; that the agents responsible for the oxidative stress were PAHs; that ultrafine PAHs penetrated the cell wall to cause such oxidative stress most easily; and that in the winter and fall, when coarse PM was associated with oxidative stress, there was a rise in PAH content in the coarse PM (presumably due to cooler atmospheric conditions). The second Li et al study

(2002b) found that while both fine and coarse CAPs were toxic, they were both considerably less potent than was DEP, suggesting the possibility that the non-DEP portions of fine and coarse PM are less toxic. Two earlier studies by Hiura et al (1999, 2000) showed that DEP caused harm to human lung cells via oxidative stress, but that carbon black (control particle) did not produce these effects, which they suggested were due to unburnt organics in the DEP. Oxidative stress, by causing inflammation, can lead to arteriosclerosis.

It is important here to emphasize that the toxicity of the coarse PM depended not upon size but upon whether the particles contained significant levels of PAHs. Similarly, a study by Veranth et al (2004) showed that while most coarse PM tested did not have biological activity, several coarse PM dusts had surprisingly large effects. This confirms the NRC statement that it is the chemical composition that causes the toxicity, not necessarily the size of the PM.

Similarly, we would point out that while the ultrafine PAHs were the most dangerous size fraction of PAHs in the Li, et al series of studies, merely being in the ultrafine size fraction doesn't necessarily confer toxicity, but rather, once again, it is the chemical makeup of the particle: Frampton (2004), for instance, found no effects in either healthy or asthmatic subjects from exposures to either 10 or 25  $\mu\text{g}/\text{m}^3$  ultrafine carbon PM.

Seagrave et al (2004) suggest that diesel particles might cause inflammatory responses that are more focused or sustained, because the particles not only induce production by epithelial cells of an inflammatory chemokine, interleukin-8 (IL-8), but also bind and concentrate the IL-8, enabling greater potential harm. Seagrave et al (2004) also report on a previous 1996 study which showed that diesel particulate matter caused oxidative changes in low-density lipoprotein, a step toward the buildup of atherosclerotic plaque in arteries.

In contrast, a review article of the extant toxicological literature on secondary sulfates (Schlesinger and Cassee, 2003) concluded that secondary sulfates are unlikely to have biological potency at ambient levels in the U.S. today.

Two recent studies showing effects of different exposures in ambient air suggest the link between these toxicology studies and epidemiology. Somers et al (2004) show that urban air near a steel mill complex in Hamilton, Ontario induced heritable mutations in a rodent model, but that rural air 30 kilometers away did not cause such mutations; that filtering the urban air to remove particles sharply reduced the mutagenicity but had no effect on rural air; and that the PAH level in the urban air was about 33 times higher in urban air than rural air, and even about 3 times higher than in the urban air of Toronto, a major city with large amounts of traffic. In showing the potential carcinogenicity of emissions from a steel mill (mutagenicity and carcinogenicity are closely linked), this study thus parallels the findings of carcinogenicity for PAHs (U.S. Department of Health and Human Services, 2002). With regard to claims (reviewed in the last section) that sulfates might be associated with cancer, this study appears to suggest that rural air – which in the Midwestern, southern, and eastern U.S. and eastern Canada always contains secondary sulfate – does not cause cancer.

Another earlier study which also may have been unjustifiably neglected is that of Cohen and Pope (1995). This study would appear to give credence to the notion that carcinogenic PAHs,

regardless of their origin (vehicular or industrial), are associated with carcinogenicity in the real world. Although this is an epidemiological study, we include it in this section because it appears to buttress the toxicology. Cohen and Pope first demonstrated the extreme carcinogenicity of emissions from coke ovens 40 years ago, showing that depending upon length of employment and location of job, the increased risk for respiratory cancer could be as high as fifteen times (relative risk or RR of 15, vs. RR of 1.06 for a  $10 \mu\text{g}/\text{m}^3$  annual increase in  $\text{PM}_{2.5}$ , in Pope et al, 2002, by way of illustrating the size of the effect). Coke of course is used in many (but not all) steel production facilities as well. Similarly, steadily increasing levels of lung cancer, rising with levels of exposure to elemental carbon (characterized as a relatively specific marker for diesel exhaust), were observed among teamsters. This study didn't measure PAHs, so while it is demonstrative of the carcinogenicity of emissions from coke ovens and facilities using coke, and from diesel emissions, PAHs are not shown definitively to be the cause of the increased lung cancers, but in light of the known carcinogenicity of PAHs, and their higher emissions from these sources, it is suggestive.

Creason et al (2001) examined changes in heart rate variability (HRV) on 24 days among 56 elderly, nonsmoking residents of a retirement center in Baltimore County, MD. The authors found a linear dose response function between higher fine PM and reduced HRV, except for two days in which the fine PM levels were the highest and third highest and were high in secondary sulfate, but were from rural Pennsylvania, in contrast to the emissions on the other days, which were characterized as being from urban or industrial areas. The authors stated that the  $\text{PM}_{2.5}$  on these 2 days "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. This study thus appears to demonstrate in the real world the same lack of toxicity of secondary sulfates that has been found in toxicology studies (Schlesinger and Cassee, 2003).

It is useful to note here, with regard to the Creason et al (2001) and Schlesinger and Cassee (2003) results, that the NRC panel also concluded that "current knowledge from toxicological studies suggests that health effects of sulfates are less than proportional to their contribution to ambient PM mass." Furthermore, the NRC study states:

"Sulfates were measured in several epidemiological studies as early as the 1970s, but no definitive conclusion was reached about their toxicity per se. One of the problems concerning these compounds is that they are among the largest components of PM, and measures of sulfates are often correlated with concentration of total PM. Correlations with other components have not been characterized; hence it is unclear whether in these early studies sulfates merely served as a surrogate for fine PM."

Finally, the report of the Government of the Netherlands (Netherlands Aerosol Programme, 2002) stated that the health-relevant particles are "...probably transport-related (diesel soot) and, more generally, combustion related primary PM emissions" (pg. 14). Additionally, the report states that "The recent results of the Dutch 7-year time-series study even suggests that lower average levels of sulfates do not necessarily lead to lower health effects in the Dutch population" (pg. 45).

## **CAPs Studies**

Several CAPs (Concentrated Ambient Particulates) studies have examined health effects from ambient particles, which are concentrated by a factor of ten or more in order to better examine potential effects of fine PM. Statistical techniques such as factor analysis are used to infer which PM components may be associated with effects, when found. While the first large scale CAPs study (Godleski et al, 2000) was published prior to April 2002, a large number of them were published later.

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 (as sulfate), 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 much higher for the S tracer (254.15  $\mu\text{g}/\text{m}^3$ ) than for the Ni (37.01  $\mu\text{g}/\text{m}^3$ ), BC (52.33  $\mu\text{g}/\text{m}^3$ ), and Si (115.44  $\mu\text{g}/\text{m}^3$ ) tracers. This finding of high mass associated with the S tracer (sulfate) is similar to that found in Godleski et al. (2000) on a typical “no-effect” day.

In a follow up study to Brook et al (2002), which found an increase in vasoconstriction in healthy human volunteers with increases in concentration of CAPs (compared to filtered air) taken from within 100 meters of a major highway, Urch et al (2004) examined which components of CAPs were significantly associated with the increase in vasoconstriction. The authors found a significant association between both organic and elemental carbon concentrations and the increase in vasoconstriction. Most elemental carbon in cities without major industrial complexes such as steel mills is related to diesel emissions, while about 40% to 50% of organic carbon in Toronto is motor vehicle related (Urch et al, 2004). Vasoconstriction could “promote cardiac ischemia in those with underlying flow-limiting obstructive lesions or could trigger instability of susceptible plaques” (Brook et al, 2002).

Another new CAPs study (Maciejczyk et al, 2005), conducted in a rural area about 40 miles north of NYC far from major traffic sources, found that the residual oil factor (2% of total fine PM mass) was associated with *in vitro* health effects. The regional (secondary) sulfate factor, (calculated at 65% of total mass, with inclusion of carbonaceous species) or a soil fraction (20% of PM mass) was not associated with health effects. This study is discussed more fully in the section below differentiating effects of secondary sulfates from primary metal sulfates from residual oil burning.

## **Newer Epidemiological Studies**

Several studies in the Atlanta area, as part of the ARIES group of studies, have utilized a much larger suite of air pollutants in examining the effects of air pollution on health. Although these pollutants are measured at central monitors, it appears that the large number of added pollutants has enabled greater specificity in pointing to sources of potential harm.

Metzger et al (2004), in a study building on the earlier work of Tolbert et al (2000), examined the relationship between ambient air pollutants and cardiovascular disease (CVD) emergency department visits. The authors found that such visits were associated with organic carbon, elemental carbon (as with the Urch et al CAPs study), oxygenated hydrocarbons (one of the added pollutants monitored), as well as with NO<sub>2</sub>, CO, and fine PM. Such visits were not associated with water soluble metals, sulfates, SO<sub>2</sub>, or acidity. Taken as a whole, these findings point to associations with vehicular emissions. EC and OC are constituents only recently routinely included in epidemiological studies. Note that in the absence of the EC, OC, oxygenated hydrocarbons, water soluble metals, and acidity, the study would have made findings not dissimilar from many other findings – showing that fine PM and some gases were associated with the CVD health effects, and not being able to either make strong associations with vehicular emissions, or negative findings on water soluble metals, which have been hypothesized to cause health impacts.

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. The authors calculated that PM<sub>2.5</sub> nonsulfate ambient exposures and/or concentrations were significantly associated with several important health endpoints, including reduction in systolic blood pressure, supraventricular ectopy (SVE) response (an arrhythmia variable), and reduction in heart-rate variability (r-MSSD). None of the PM<sub>2.5</sub> sulfate concentrations or exposures were significant for these endpoints. Because of the small number of subjects and low sulfate levels (mean level of sulfate = 2.0 µg/m<sup>3</sup>, about equivalent to levels in New England in 2001-2003, and about ½ to 1/3 levels in the Midwest in that time frame), the authors view their findings as preliminary and also suggest that the study be repeated in areas where secondary sulfate levels are higher.

### **Studies Distinguishing Effects of Secondary Sulfates from Primary Metal Sulfates**

Residual oil is used to produce electricity in or near only a few cities in the U.S. today, but two and three decades ago such use was more widespread. Since a major emission from residual oil use is primary metal sulfates (mostly of vanadium and nickel), the possibility arises that health effects attribute to “sulfates” might be due to either secondary sulfates (ammonium sulfate or bisulfate), or alternatively to primary metal sulfates. One example of such a study appears to be that of Laden et al (2000), where a finding was suggested between sulfates and elevated risks of mortality, and between a tracer for coal emissions (selenium) and elevated mortality risks, for only one of six cities (Boston). Virtually all particles due to coal plant emissions are secondary sulfate. Grahame and Hidy (2004) demonstrated that although levels of both sulfate and selenium were low in Boston (selenium was lowest of the six localities, sulfate fourth highest of six), only in Boston was there a source other than coal for either selenium or sulfate: a significant amount of both selenium and sulfate in Boston came from local residual oil fired power plants, and much of the sulfate from the oil-fired power plants was primary metal sulfate. The authors showed that toxicology studies found secondary sulfates were not harmful at ambient levels, but that primary metal sulfates likely were harmful. Thus the reason that neither sulfate nor selenium as a marker for coal-plant emissions were found significant in the other cities appears

to be that these emissions were associated with harm only when they were emitted from residual-oil fired sources, with harmful primary metal emissions.

This finding appears to be corroborated in another recent study, Maciejczyk et al (2005). This study is one of a group of nine studies devoted to health effects of chronic exposure to PM done by the NYU School of Medicine, and published in the April/May 2005 issue of *Inhalation Toxicology*. Studies associated with that of Maciejczyk et al (2005), using both normal mice and knockout mice modified to be prone to develop atherosclerotic plaques, had exposed the mice to five months of CAPs in an area about 40 miles north of New York City. Maciejczyk et al (2005) examined in a parallel, simultaneous study whether individual constituents of fine PM might have caused an observed increase in human bronchial epithelial cells of Nuclear Factor kappa B (NF- $\kappa$ B). NF- $\kappa$ B is part of a family of transcription factors which are “persistently active in a number of disease states,” including chronic inflammation, cancer, and heart disease, activation of which “is indicative of the oxidative stress that eventually triggers the release of various cytokines.” They found that the oil combustion source category was significantly correlated with the NF- $\kappa$ B assay, with nickel and vanadium (emissions primarily from oil-fired power plants) also associated with the NF- $\kappa$ B assay. Regional sulfate was not found to be significantly associated with the assay. This result was found despite the fact that the oil combustion source contributed only 2% to total mass, while the regional (non-metallic) secondary sulfate category contributed 65%.

Maciejczyk et al (2005) also speculate that “Our results may also help to explain why the Northeastern population exhibits greater PM-related mortality impacts than other parts of the country.” This observation was repeated by Lippmann et al (2005) in the concluding of the nine studies:

“The fact that the oil combustion source contributed only ~ 2% of the PM<sub>2.5</sub> mass is notable, as is the lesser degree of correlation with other, much larger sources of the PM<sub>2.5</sub> mass. If the inflammatory response influences cardiac as well as pulmonary system responses related to indices of health, it may account for the greater mortality coefficient in the northeastern United States, where residual oil combustion is concentrated, than in the rest of the country in the NMMAPS time-series study....”

These studies corroborate an early 2002 source apportionment study by Janssen et al, which broke new ground by demonstrating that central air conditioning modified the effects of pollution, by minimizing exposure to outdoor air pollution. Janssen et al found that among the sources examined, only residual oil fired sources, highway sources, and diesel sources were associated with hospital admissions for CVD. With regard to highway sources and diesel sources, these findings parallel those of Metzger et al, but since Janssen et al utilized data from 14 cities, some of which are near residual oil sources, they also found associations with residual oil.

These findings may have direct use in understanding some of the findings in the Draft Staff Paper. In Figure 3-1, the associations for the Tsai et al study for three localities are presented. For the two industrial cities, Newark and Camden, PM is significantly associated with a variety of endpoints. For the nearby suburban location, Elizabeth, PM is not so associated. Sulfate

levels were virtually the same in the three locales, but the oil burning coefficient was highly significant for both Camden and Newark, but not for Elizabeth (Table 4 in Tsai et al, 2000). This suggests the possibility, again, that it isn't sulfate per se that is harmful, but rather primary metal sulfates from oil combustion.

### **Studies Which Attempted to Distinguish Health Effects Among PM<sub>2.5</sub>, Sulfates, and Acidity**

Attempts were made, even with the small number of pollutants used in most studies, pre-2002, to discover which pollutants had the more important associations with health effects: sulfate, acidity (which accompanies secondary sulfates), or the fine PM mass of which sulfates and acidity are part. Although neither study below is recent, it is useful and still pertinent to review their findings here. Both studies (Dockery et al, 1992; Lippmann, et al, 2000) hypothesized that the smaller and more acidic the particle, the larger and more significant would be the health effect association; in each study, the opposite was found. In Dockery et al (1992, the authors found that PM<sub>10</sub> was significantly associated with increased daily mortality, and that fine PM was near significance, but that both sulfate and acidity were far from significance. For Lippmann et al (2000), 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<sup>+</sup> and SO<sub>4</sub>." Thus, even during an era when relatively few pollutants were monitored, and before exposure gradient studies were introduced, analysts hypothesizing that sulfates and acidity were the causative agents within fine PM found the opposite. Results of these studies might have seemed curious when published. However, in light of the new studies (1) differentiating toxicology of secondary sulfates from toxicology of other particles; (2) separating effects of sulfates from those of different particles in CAPs studies; (3) using more sophisticated epidemiology and a greater number of pollution variables to better separate effects of sulfates from those of pollution from different sources; and (4) separating effects of seemingly toxic primary metal sulfate emissions of residual oil sources from effects of secondary sulfates, these studies can now be seen as more meaningful and should be reconsidered.

### **How do These New Studies and New Findings Relate to the Draft Staff Paper's Examination of Health Effects of Fine PM?**

These studies, the great majority of which have been published after April 2002, form a substantial new body of evidence which enables us to do what we could not do in April 2002: point to specific sources and types of pollution which more advanced epidemiological approaches (exposure gradient studies, but also others) as well as toxicology suggest are harmful to the public health, and which sources and types of pollution may pose little threat of harm.

These studies in aggregate suggest that emissions from vehicles (primarily diesels), from certain industrial sources (those which emit PAHs at a minimum), and residual oil plants have been harmful and are likely the cause of health effect associations in the epidemiology literature. These studies also suggest that secondary sulfates at concentrations found in the U.S. appear not to cause large health effects.

The Draft Staff Paper puts great emphasis on the two major cohort studies of the long term effects of PM, the 6 Cities Study (Dockery et al, 1993) and the American Cancer Society (ACS)

studies (Pope et al, 1995; update Pope et al, 2002). Both the 6 Cities and ACS studies are multi-city, central area monitor studies, and both monitor a minimum of pollutants: for particles, only PM of different size fractions and sulfate (plus acidity for the 6 Cities study). Thus important industrial and vehicular emissions, especially PAHs, as well as elemental carbon and organic carbon and other emissions, were not measured.

The evidence in the new studies reviewed above allow us to comment on the findings of these two studies, based upon the new understanding about specific components of pollution.

### *6 Cities Study*

This study measured the PM and sulfate levels of the six localities chosen, and related these measurements to mortality rates in the study locations. Sulfate and PM had an extremely high correlation of 98%, so unsurprisingly, health effects found for one were found for the other, as suggested by the NRC (above). The “adjusted mortality risk ratio for the most polluted of the cities as compared to the least polluted was 1.26...” The study found elevated risks for dying from lung cancer and cardiopulmonary disease but not other causes considered together.

The city with the highest pollution was Steubenville, Ohio, a major industrial center, with “primary and secondary metal processing plants, coke plants, [and] chemical plants...proximal to the...site” (Spengler and Thurston, 1983). In addition, 600 acres of coking facilities were about 3 miles downriver, and the industrial center of Weirton, West Virginia, about 3 miles upriver.

In contrast, the city with the lowest PM and sulfate levels was Portage, Wisconsin, population 8,000 and described as “a commercial center for...farming communities” (Spengler and Thurston, 1983).

It isn't a surprise that the air in a major industrial center with the kinds of operations and pollution control found in 1980 would be more harmful than the air of a small farming town. But because specific known harmful constituents of PM – such as PAHs – were not measured, we cannot know the strength of association with these toxic emissions. If toxicologists were asked whether it was more likely that increased rates of lung cancer and heart disease would be associated with PAHs, or with secondary sulfates, it is unlikely they would chose sulfates, given the known toxicology of both, reviewed above. But the 6 Cities study did not offer a choice, because it failed to measure concentrations of PAHs or of other potentially harmful emissions.

### *ACS Study*

The larger ACS study makes similar findings and has similar issues. A reanalysis by the Health Effects Institute (HEI) in 2000 found, in Appendix B (Table B.11), that there were differences in exposures to occupational lung carcinogens between men (high) and women (low), and between those with better than a high school (HS) education and those with less education (Krewski et al, 2000). In the updated ACS study (Pope et al, 2002), heightened risks for lung cancer in the disaggregated analysis were found for men, but only for those men with less than a HS education, and not for women of any educational level. The elevated risks by sex and education

levels thus exactly matched the profiles for exposure to occupational carcinogens in Krewski et al (2000). But Pope et al (2002) failed to note the findings in Appendix B of Krewski et al (2000), leaving readers unknowledgeable about the patterns of exposure to occupational carcinogens. In the aggregated analysis, Pope et al (2002) found an overall increased risk for lung cancer (when both sexes and all educational groups are combined) associated with PM and with sulfate, as in the 6 Cities study. But again, toxicologists would be unlikely to agree that secondary sulfate, or all fine PM regardless of chemical makeup, would be more likely to cause lung cancer than exposure to known industrial carcinogens, especially if the pattern of exposure for carcinogens were known to match the pattern of heightened risk.

Now that we understand the size of the risks of exposure to vehicular emissions, we should be able to find such risks in the ACS study. These risks are primarily cardiopulmonary, according to the exposure gradient studies. Pope et al (2002) did find elevated risks for cardiopulmonary disease in the overall risk (when both sexes and all educational groups are combined), but did not find any increased risks for those with better than a high school education, when educational levels were examined separately. Since most of the ACS cities were in the Midwest/Southeast/Eastern parts of the U.S., where secondary sulfates are never absent, such people would be exposed to secondary sulfate – but apparently, if the results by educational level are to be believed, are not at risk from such exposure. What could account for this?

People with higher socioeconomic status tend not to live near major roadways. Reynolds et al (2001) found that families earning more than \$56,000 annually had only one-seventh the traffic passing within 165 meters of their home than did families making less than \$18,000. This dichotomy might well be larger if the analysis had considered diesel traffic within 165 meters of one's home. While higher socioeconomic status (as measured by either higher educational levels or higher income) is likely to confer reduced risk by itself, it is unlikely to bring the risk of exposure to an air pollutant that might cause cardiopulmonary death in others to zero. The ACS study thus offers a choice: would a toxicologist believe the overall raw findings, suggesting links with cardiopulmonary mortality for everyone for exposure to fine PM and sulfate, even with toxicology suggesting no harmful effects from secondary sulfates? Or would it make more sense to believe the findings broken down by education, where those with higher socioeconomic status have no association between pollution and health (even with exposure to secondary sulfate), given our understanding that those with higher education are exposed to far less vehicular emissions where they live, and thus are exposed to far less of the toxicologically harmful ingredients that are most strongly concentrated near such roads?

The issues raised by the Krewski et al (2000) reanalysis, which go well beyond the issue of occupational exposure to lung carcinogens, do not appear to have been adequately dealt with in the Draft Staff Paper. In a critique of the ACS study within a critique of a draft of the Criteria Document, the National Research Center for Statistics and the Environment (NRCSE, 2001) pointed out that when historical measures of PM are included in the model for the 6 Cities study (in Krewski, et al, 2000), in order to account for the possible effect on mortality today from higher levels of pollution in the past, the estimated relative risk of adverse effects during the study period drops in half.

Thus a question: what would have been the effect for the ACS study, had air pollution data for the past been available? Would the low RR of mortality (1.06) for an increase of  $10 \mu\text{g}/\text{m}^3$  in annual  $\text{PM}_{2.5}$  levels have also been cut in half, and perhaps become insignificant? The NRCSE: “This kind of sensitivity, to how the historical PM variable is treated, underlines the extreme difficulty of separating short-term and long-term effects in this kind of analysis.”

The NRCSE stated, “The draft PMCD seems to have concluded that the HEI reanalysis ended up confirming all the major claims that were made in the original HSC [Harvard Six Cities] and ACS analyses. However, careful reading of the re-analysis shows that there are in fact numerous very important issues of methodology and interpretation, to which the re-analysis certainly made significant contributions, but which cannot be considered resolved at the present time. They may never be.”

The NRCSE also raised in this 2001 review the same issue that the NRC raised three years later. NRCSE states, “There are several studies in which the PM effects disappear when other pollutants are included in the model. There are also several studies with the opposite result. In our opinion, the most severe problem is that we do not yet have a firm grip on the composition of particulate matter in different parts of the United States. The criteria document authors seem to expect that health effects of particulate matter is a matter only of the size of the particles; not of the chemical composition of the particles.”

We suggest that some of the difficulties the NRCSE wrestled with in 2001 – and indeed, EPA wrestles with today – could be resolved, if results of the newer studies (post April 2002) are considered in this review of the health effects of PM.

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