COMMENTS OF DEPARTMENT OF ENERGY/OFFICE OF FOSSIL ENERGY STAFF ON JUNE 2003 FOURTH EXTERNAL REVIEW DRAFT CRITERIA DOCUMENT FOR PARTICULATE MATTER

Summary and Conclusions

The Fourth External Review Draft Criteria Document for Particulate Matter (henceforth, the CD) is a very comprehensive review of both epidemiological and toxicological research into the health effects of particulate matter (PM) in ambient air. DOE/Office of Fossil Energy offers the following comments on it.

OMB's "Principles and Procedures" memorandum to agencies states:

> "OIRA's [OMB's Office of Information and Regulatory Affairs] review also evaluates, on occasion in consultation with the Office of Science and Technology Policy, whether the agency has, in assessing exposure to a risk or an environmental hazard, conducted an adequate risk assessment. The risk assessment should be an objective, realistic, and scientifically balanced analysis."

Risk assessment cannot easily be separated from the issue of relating actual exposure to health outcomes. Throughout, the CD recognizes the importance of relating exposure to a pollutant or group of pollutants, with health impacts. In addition, on pg. 8-29 the CD notes the importance of large exposure gradients as a way of examining the health impacts of pollutants.

By far the largest exposure gradient which has been observed in any short-term or long-term statistical study associating pollution and adverse health outcomes is the exposure gradient from the mid point of a large roadway, to distances tens to a few hundred meters distant. Concentrations of vehicular PM, elemental carbon, black carbon, carbon

monoxide, and ultrafines can vary by more than an order of magnitude within these short distances.[1] Visually, these concentration peaks resemble a steep "A frame" (Figs. 1 and 2).

There is now a growing body of research which relates exposure to the high levels of emissions in close proximity to major roads, with adverse health outcomes. This is in contrast to using measurements from one or a few central monitors, as the great majority of previous studies have done, and implicitly assigning such concentrations to everyone living in a given city, country, or SMSA (standard metropolitan statistical area).[2] Additionally, there are a number of toxicological studies, many of them relatively new, which assess biological mechanisms of various components of highway emissions.

On December 4, 2001, the Administrator of OMB's OIRA urged EPA to pursue research that evaluated the relative toxicity of different types of particles to determine "those particles most responsible for health risks." Nevertheless, the CD does not analyze or reference any of this body of research. Studies not analyzed include those:

(1) Demonstrating the "A frame" of vehicular emissions (Zhu et al, 2002a and 2002b [Fig. 1]; Netherlands Aerosol Program, 2002 [Fig. 2]).
(2) Examining health impacts of living or working in close proximity to major roads (Hoek et al, 2002; Mann et al, 2002; Herbert et al, 2000; Stern et al, 1988; Janssen et al, 2003; Venn, A. J. et al. 2001; Nicolai et al, 2003; Lin et al, 2002; Buckeridge et al, 2002; English et al, 1999; Brunekreef et al, 1997; van Vliet et al, 1997; Netherlands Aerosol Program, 2002; Wilhelm and Ritz, 2003).
(3) Examining the toxicology of various roadway emissions, all of which are highly correlated, suggesting that health impacts from close proximity to major roads *could be attributed to either PM or gaseous components* (Thom et al, 1999; Anderson el al, 1973; Allred et al, 1989; Allred et al, 1991; Hiura et al, 1999; Hiura et al, 2000; Li et al, 2002a and 2002b; Li et al, 2003; Huang et al, 2003).

[1] Although not measured in Figs. 1 and 2, other vehicular emissions -- NO2, semi-volatile organic compounds (SVOCs), polycyclic aromatic hydrocarbons (PAHs) -- are likely to exhibit similar "A frame" concentrations.

[2] This comment has applicability to any of the methods for developing statistical associations, including factor analysis, on the grounds that if we aren't measuring what people are actually exposed to – with regard to highly variable pollutants – then the answer from the model, no matter how sophisticated it might be, may point in the direction of the wrong pollutants, as explained in the text of these comments.

Yet this body of literature offers, in our view, the first group of studies which can relate a gradient of exposures to a particular source of pollutants, to a variety of health impacts. Exposure of individual people is much more precisely measured than in studies using data from central monitors. For example, the Hoek et al (2002) cohort study finds that the relative risk (RR) of cardiopulmonary mortality for those aged 55 and over, living within 100 meters of a thruway or within 50 meters of a major urban road, is almost double (1.95). This RR is strikingly large, in comparison to other cohort studies, using pollution measures from area monitors. The gradient of exposure in these highway proximity studies is quite large, as are the health effect associations.

The CD recognizes that vehicular emissions may have a more important role in health associations than previously thought. For example, the CD quotes from the Janssen et al (2002) study:

> "There were also significant positive relationships between CVD effects and PM_{10} percent emissions from highways or from diesel vehicles, *suggesting that mobile source particles may have more potent cardiovascular effects than other particle types*." (emphasis ours)

Clearly more research remains – we make recommendations below. Yet enough has been done to demonstrate that historically these highway emissions likely were responsible for a larger portion of observed health outcomes than previously thought (most epidemiological studies, especially long-term cohort studies, relate air pollution data from the 1970s, 1980s and 1990s to health impacts of the time). Furthermore, as vehicular emissions have changed over time (carbon monoxide emissions on the highway are down by over an order of magnitude since 1975), it is crucial to understand what the effects of future vehicular emission profiles might be.

Furthermore, insights from the "highway proximity" studies above allow us to make new interpretations of important long-term studies, such as the ACS study update (Pope et al, 2002). In the text below, we use internal evidence in the ACS study, in combination with the highway proximity analyses, to suggest that the great majority of the mortality observed

in the ACS study may be attributable just to vehicular emissions (the study period was 1982 through 1998), and that regional PM emissions may have little or no toxicity. We also suggest that the findings of the Six Cities study (the other long-term study upon which EPA places most reliance) demonstrate that specific types of PM may have more toxicity than other types, as suggested by the National Research Council in 1998 (National Research Council, 1998).

In addition, the ability of short-term epidemiological studies (virtually all of which use emissions data gathered from one or a few area monitors) to attribute health outcomes to particular pollutants is also limited by their inability to incorporate proximity to heavy traffic into their statistical associations.

We also review in the body of our comments statements from the recent Health Effects Institute review of the GAMS statistical issues surrounding the NMMAPS study. These comments suggest that the difficulties with the GAMS issues, the reduced effect levels found with the NMMAPS reanalyses, and the finding that different model choices have substantial impacts on effect levels derived, all tend to focus more emphasis on long-term studies and on toxicological studies.

The CD also does not analyze or reference several other important and relevant new studies related to toxicity of particles more relevant to non-vehicular emissions, including the 37-page review of toxicology studies of secondary sulfates and nitrates (Schlesinger and Cassee, 2003).

There are dozens of articles cited in Chapters 7, 8 and 9 in the CD that have been published in late 2002 or up to May 2003 -- including two in press, not yet available. Therefore we do not understand why the articles that have been omitted, but which are published in the same time frame – including particularly the entire group of articles evaluating the morbidity and mortality impacts of living in close proximity to heavily trafficked roadways, the toxicity articles cited above, as well as the Schlesinger and Cassee article -- are not cited and evaluated in the CD.

We believe that analysis of these studies will likely lead to improved insights for understanding what types of PM (or associated gases) may have harmed public health in the past (when some types of emissions were over an order of magnitude higher than today), thus effecting our interpretation of important studies, and looking forward, what types of PM (or associated gases) might still be harming the public health.

EPA can continue to take the viewpoint[3] that any type of PM is likely to be harmful to human health at ambient levels unless it can be "ruled out." However, this is likely to be impossible as long as high-dose *in vitro* or *in vivo* analyses, or conflicting epidemiological studies, are the standard for eliminating pollutants from consideration.

Alternatively, EPA could use analysis to decide whether certain types of PM, or PM sources, have negligible effect on human health at ambient levels, compared to other types of PM which may have important effects. This approach would appear to protect public health better than one which regulates any and all PM as if they were all roughly equally toxic.

One possible way to do this is to use "standardized regulatory toxicology," an approach we recommended in our comments on the 2002 CD for Particulate Matter. Instead of using toxicology only as a means of discovering or testing hypotheses, it could be used as a way to determine which types of PM, or sources of PM, are likely to have negligible, or important, health impacts at ambient levels. "Standardized regulatory toxicology" would test each pollutant type, or mix, of interest. Tests would use the same multiples of current ambient mean levels for each pollutant type or mix: e.g., a rural sulfate/nitrate/organic mix; roadside PM mixtures; ROFA; clean burning diesel and gasoline vehicular emissions; "dirty" diesel and gasoline emissions; various industrial emissions; and fractions of each (e.g., ultrafine PAHs and SVOCs, CO, roadside tire and brake component PM, etc.). Each of these, and many more PM types, would be tested against each health endpoint deemed

[3] See for example, pg. 9-52 in the CD.

relevant, at ~ 10, 40, 150, 500, and 1000 times ambient levels in animal models – for example, heart rate variability, blood viscosity, specific types of inflammation – once toxicologists have decided which of these tests seems more relevant to human health endpoints of concern. Some of these tests might produce meaningful effects at 10 times mean ambient levels, some might not produce effects until 1000 times ambient levels. In such a case, regulation of the first PM type or mixture would be more likely to protect public health than regulation of the second.

In conclusion, we note that EPA has successfully sponsored hundreds to thousands of useful studies, but now can usefully move to different phases of analysis. We recommend that EPA:

1. Sponsor and use studies which relate human exposure to specific sources of emissions with emission gradients, rather than only using studies which relate pollution levels measured at one or more central monitors to the population of an entire city, county, or SMSA.
2. Use toxicology to a greater extent than previously to help interpret epidemiological results.
3. Reanalyze existing studies in light of new findings from (1) and (2) above (see examples in text below).
4. Consider using "Standardized Regulatory Toxicology" as a method to determine relative toxicity of ambient pollutants; and
5. Determine which types of PM or associated gases are likely to have meaningful public health impacts at realistic ambient concentrations, and which are likely to have negligible impacts, and regulate on such a basis.

Introduction

The CD is a very comprehensive review of both epidemiological and toxicological research into the health effects of particulate matter (PM) in ambient air. In many ways, it improves upon the already impressive previous CDs. For example, the explanation of the differences between different types of epidemiological studies (section 8.1.2) is both clear and useful. Also, the authors of the CD appear to have spent considerable effort to make the CD more clearly understood than in previous years, no easy feat considering that literally thousands of studies are referenced and discussed.

The CD recognizes the most important question facing researchers and those concerned with the health impacts of air pollution: what types of PM (or associated gases) may be causing adverse health impacts? This was the concern of the CASAC (Clean Air Scientific Advisory Committee) review in 1996, of the New England Journal of Medicine in 2000 (Ware, 2000), and of the NRC (National Research Council, 1998) review in 1998.

The CD also explicitly recognizes that in some CAPS (Concentrated Ambient Particles) experiments, adverse health effects were observed on some days, but did not occur on others, and that the researchers concluded that the absence of health effects on certain days was due to the absence of particular types of PM. For instance, on pg. 7-49, the CD explicitly notes that Gordon et al (1998) found that the "effect did not appear to be [CAPs] dose-related and did not occur on all exposure days, suggesting that day-to-day changes in particle composition may play an important role in the systemic effects of inhaled particles." The CD also states on the same page that Godleski et al (2000) also found that the heart rate effects were not observed on all exposure days, but doesn't note that Godleski et al (2000) explicitly state in their report that the absence of effect was likely due to absence of the toxic PM fraction. Similarly, on pg. 7-48, the CD states that changes in heart rate variability were found only on 10 of 23 exposure days.

In addition, in a study of heart rate variability in elderly subject, Creason et al (2001) find that on two of the 24 days of their study, there was no heart rate variability; on only those days, the concentrations of $PM_{2.5}$ were the highest and third highest among the 24 days; only on these days, however, was the air mass from rural Pennsylvania (as opposed to urban and industrial sources); and that the lack of variability was likely due to the difference in makeup of the $PM_{2.5}$. We discuss this study more fully below.

Thus, the CD implicitly acknowledges that if we fail to identify what types of PM_{10} and $PM_{2.5}$ (and/or associated gases) are responsible for adverse health effects, notably increased risk of premature mortality, as well as respiratory and other morbidity effects,

then the controls that will result from PM regulations may not necessarily control the pollutants that cause the problems.

There are at least two general, but opposite, approaches to deal with the dilemma of isolating the most toxic, and the negligibly toxic, types of PM, for the purposes of regulation under statues designed to protect the public health.

One approach is to utilize the best research available, and to prioritize types of PM (and, where appropriate, associated gases) for control, based upon the best knowledge available, and to separate negligibly toxic pollutants from more toxic pollutants, for the purpose of protecting the public health.

The opposite approach would be to continue to assume that all PM_{10} and $PM_{2.5}$ is harmful, and regulate all PM on that basis, unless it can be demonstrated to an extremely high degree that a particular PM fraction is harmless. The latter appears to be EPA's approach, based upon statements in the CD, and public statements by EPA officials. But epidemiological studies, often ambiguous, have found associations with virtually any type of PM, and a toxicological test of a PM fraction at several orders of magnitude above ambient levels is almost sure to find some type of potentially adverse effect, no matter how subtle. So attempting to "rule out" types of PM is likely to be a fruitless exercise. Nevertheless, this is the approach being taken in this CD. For example, on pg. 9-52, the CD states:

> "Inherent in the NRC research agenda (NRC, 1998) was the consideration that one, or perhaps a few, characteristics of PM would be associated with toxicity, and exposure monitoring could concentrate on these components. However, such narrowing of focus is not yet possible, given the wide array of PM characteristics that have been found to be associated with toxicity either through epidemiological or toxicological studies…."

Is there evidence that could help EPA support the first approach, e.g., identifying the most harmful components of PM (and associated pollutants)? And is there evidence that

would enable EPA to find that certain components of PM may have negligible toxicity at ambient levels?

While additional research is needed, we suggest that such evidence is currently available.

Much of it is in research literature not cited or utilized in the CD, some of it is in references included in the CD, and some of it comes to the fore when reanalyzing existing studies in light of the literature not cited or utilized. There are dozens of articles cited in the CD that have been published in late 2002 or up to May 2003 -- including two in press, not yet published. Therefore we do not understand why the articles that have been omitted, but which are published in the same time frame – including particularly the entire group of articles evaluating the morbidity and mortality impacts of living in close proximity to heavily trafficked roadways -- are not cited and evaluated in the CD.

The CD recognizes the importance of relating exposure to a pollutant, or a group of pollutants, with health impacts. The current CD states (pg. 8-29):

> "In general, for those studies not clearly flawed and having adequate control for confounding increasing scientific weight should be accorded to in proportion to the precision of their estimate of a health effect. Small studies and studies with an inadequate exposure gradient generally *produce less precise estimates than large studies with an adequate exposure gradient*." (emphasis ours)

By far the largest exposure gradient we have observed in any short-term or long-term statistical study associating pollution and adverse health outcomes is the exposure gradient from the mid point of a large roadway, to distances tens to a few hundred meters distant. We discuss this issue in the next section.

Additionally, the CD notes in several places that vehicular emissions may be more toxic than other emissions, even without evaluating the studies examining health impacts for those living in close proximity to heavily used roads. For example, the CD notes findings of Janssen et al (2002):

> "…separate analysis for nonwinter-peaking and winter-peaking PM_{10} cities yielded coefficients for CVD-related hospital admissions that decreased significantly with increased percentage of central AC for both groups of cities. There were also significant positive relationships between CVD effects and PM_{10} percent emissions from highways or from diesel vehicles, *suggesting that mobile source particles may have more potent cardiovascular effects than other particle types*." (emphasis ours)

Thus it is puzzling why the CD does not contain or analyze studies relating pollution outcomes to exposure within the gradient of highway emissions, to exposure farther away. This is especially true given the emphasis on exposure gradients in the current CD, and given the CD's apparent tentative embrace of the notion that vehicular emissions may be more toxic than others.

New Spatial Understanding of Pollution Variation and Associated Health Impacts

One of the difficulties in understanding which types of pollutants may be harmful in ambient air has been that we do not have a good idea of what amounts of which pollutants people have been exposed to in the hours or perhaps days before they become ill. Traditionally, studies utilized either one or a few central monitors to measure pollution concentrations, which have been assumed to represent the exposure levels for people in the entire city. For instance, the initial ACS study explicitly states that the use of central monitors to measure pollution levels means that any important local variation in pollution would be missed.[4]

Over time, researchers increasingly recognized that there was some amount of spatial variability in pollution levels, not just between $PM_{2.5}$ levels in rural areas and city centers (where pollution levels are higher), but also within a city. Nevertheless, most epidemiological studies (including source apportionment studies, such as those using factor analysis) continued to utilize data from one or a few central monitors, and thus do

[4] "Sulfate and fine particulate pollution data for a large number of communities are only available from central site ambient air pollution monitoring networks. These data can estimate variability in pollution exposure between communities, but within-community spatial variability of sulfate or fine particulate concentrations cannot be estimated for most of the areas included in this study." (pg. 291, Pope et al, 1995)

not have the ability to relate variability in actual air pollution exposures to health outcomes.

Starting only recently, however, researchers have come to understand that pollutants from at least one particular source type – various vehicular emissions – can vary by a factor of over an order of magnitude within 100 to 200 meters of a major road. Two recent studies (Zhu et al, 2002a, 2002b) showed that the number of the smallest ultrafines decreased by a factor of 30 within a few hundred feet of a major freeway. CO and other ultrafine PM levels 17 meters downwind of the highway were 10 times higher, and black carbon particles 6 times higher, than 300 meters downwind of the freeway, with most of the reduction in the first 100 meters. Although these studies did not measure NO_2, it is expected that levels of this pollutant would also be significantly higher nearer the roadway. Fig. 1, from Zhu, et al, shows that visually, this extreme spatial variation in pollutants looks like an "A frame." Thus the personal exposure to a panoply of vehicular emissions of an individual who lives in close proximity to a major urban road or a thruway may be many times higher than that of an otherwise similar individual who lives half a mile from such a road.

In roughly this same time frame, researchers undertook to study the health effects of vehicular emissions not by attributing measurements of pollution at one or more area monitors to all the people in the city, but rather to comparing health effects for those living in close proximity to major roads, to those not living in close proximity.

In general, these studies found very high risks of mortality or morbidity for those living in close proximity to major roads, generally much higher than those found in studies using a single monitor. The risks cannot be attributed at this time to any one or more type of vehicular emission. It appears likely, based upon toxicology (see below), that CO, ultrafines, as well as other types of vehicular emissions may have roles in causing adverse health impacts.

The CD recognizes the importance of relating exposure to a pollutant, or a group of pollutants, with health impacts. The current CD states (pg. 8-29):

> "In general, for those studies not clearly flawed and having adequate control for confounding increasing scientific weight should be accorded to in proportion to the precision of their estimate of a health effect. Small studies and studies with an inadequate exposure gradient generally produce less precise estimates than large studies with an adequate exposure gradient."

By far the largest exposure gradient we have observed in any short-term or long-term statistical study associating pollution and adverse health outcomes is the exposure gradient from a large roadway to a few hundred meters away.

To the extent that studies using one or more area monitors (instead of highway proximity) attribute mortality in larger cities to higher PM_{10} and/or $PM_{2.5}$ levels, a higher mortality rate in such areas actually due to vehicular emissions (and perhaps local industrial emissions in some cases) might be attributed instead to PM_{10} or $PM_{2.5}$ mass measurement. This is because the larger cities, which generally have higher vehicle miles traveled per square mile, also have elevated PM levels, due to the addition of PM from local sources (including mostly vehicular as well as industrial in most cases) to PM from regional sources. This issue is discussed in greater depth below.

Because sulfate is highly correlated with PM, such studies often find associations between sulfate and health endpoints as well. For example, in the "Six Cities" study (Dockery, et al, 1993), $PM_{2.5}$ and sulfate have a 98% correlation (calculation in Krewski et al, 2000). High PM/sulfate correlations are to be expected in the eastern U.S., where historically sulfate has been 30% to 40% of $PM_{2.5}$ concentrations. Even in the ACS study, which includes many cities from the western U.S., where sulfate levels are low, $PM_{2.5}$ and sulfate have a correlation of over 70% (Krewski et al, 2000).

None of these mostly newer studies, all of which are discussed below -- e.g., those associating proximity of one's home to highway traffic with morbidity or mortality -- is either utilized or cited in the CD, as far as we could determine in reading either the text or

the reference lists at the end of chapters 3, 7 (Toxicology), 8 (Epidemiology), or 9 (Integrative Synthesis) in the CD; neither are the Zhu et al (2002a and 2002b) studies, which show the extreme local variability in pollution near highways. Nor is the recent report of the Netherlands Government (Netherlands Aerosol Program, 2002), which among other findings also shows that modeled highway PM_{10}, $PM_{2.5}$ and elemental carbon (EC) levels rise by an order of magnitude or more between a highway and 100/200 meters distance from the highway (Fig. 2), confirming the measurements of Zhu et al (2002a, 2002b). Together, these three studies demonstrate the extreme local spatial variability of various types of PM and gaseous vehicular emissions, all highly correlated with each other.

These "highway proximity" studies appear to be the first studies to offer a significant improvement in our ability to attribute health impacts to particular types of pollution, based upon exposure rather than use of area-wide monitors, which can't measure large or extreme local pollution variability. To the extent such studies are absent from the CD, the adequacy of the CD to provide an adequate understanding of the health impacts of PM and associated pollutants may be significantly impaired. We list and discuss many of these studies below.

Specific Non-Toxicological "Highway Proximity" Studies not Included in CD

Cardiopulmonary-Related Morbidity and Mortality Findings

There have been a significant number of recent publications (about half in the last 15 months) which examine the health impacts on people living or working in close proximity to major urban roads or freeways, which attempt to approximate pollution concentrations at peoples' homes by interpolating between monitors and then associate health outcomes with approximated pollution levels, which examine the toxicology of various vehicular emissions; and which measure concentrations of different pollutants at different distances from major roads. We review these studies and their findings below. Except where noted, they do not appear to be included in the CD.

A recent long-term study of chronic health effects, using data from a cohort study that began in 1986, examined the relationship between premature mortality and distance of residence from sources of vehicular emissions (Hoek et al, 2002). It found that those aged 55 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 (relative risk = 1.95, CI = 1.09 – 3.52) than those living further from roadways. For all-cause mortality, the relative risk was 1.53 (CI = 1.01 - 2.33) and was statistically significant for the "living near major roadway" mortality variable when the association was derived for those living at their 1986 address for 10 years or longer. This suggests a longer-term, chronic effect of living near a major roadway.

Although the authors find nearly identical associations between risks of higher mortality and both black smoke[5] and nitrogen dioxide levels, the authors do not attribute the excess mortality to any specific pollutant(s), but rather to vehicular emissions generally. They also point out that ultrafines are much higher very close to highways, but provide no measurements, nor do they measure CO.

A relative risk of 1.95 for cardiopulmonary mortality is far larger than the relative risks found in earlier studies of chronic PM effects, which typically have: (a) only one or a few monitors per city; (b) relate elevated mortality risks to the pollution levels recorded at that such a monitor or monitors; and (c) are generally insensitive to elevated mortality adjacent to major roads. For example, the recent ACS update (Pope et al, 2002 – included in the CD) finds a significant association between $PM_{2.5}$ and cardiopulmonary mortality, with an overall relative risk of only 1.06 for a 10 $\mu g/m^3$ increase in ambient $PM_{2.5}$. (For comparison, an annual increase of $PM_{2.5}$ of 10 μg/m3 is roughly equivalent to the difference in $PM_{2.5}$ levels between a "clean" medium-sized city and a "dirty" large one.)

[5] Black smoke is a variable used in Hoek et al, 2002; black carbon is a variable measured near freeways by Zhu et al, 2002a, 2002b.

The finding of a small $PM_{2.5}$ relative risk (e.g., 1.06) in the ACS study, in contrast to relative risks about 15 times larger (e.g., 1.95) for the same health endpoint (cardiopulmonary mortality) in the Hoek, et al (2002) highway proximity study, raises an important question: how much of the mortality reported in these older studies might be due to highway-related pollution within each locality? Local vehicular emissions from major roads add significantly to the overall $PM_{2.5}$ levels in a city. How much of the increased mortality in larger, more populated areas might be due to decedents living in close proximity to the highways; how much might be due to other important local sources (perhaps steel mills, as in Utah valley, or primary metal emissions from residual oil combustion); and how much might be due to impacts of regional $PM_{2.5}$, with a different composition?

A recent study of carbon monoxide levels in Los Angeles (Mann et al, 2002) finds that a 1 ppm increase in the estimated 8-hour CO levels to which a person is exposed at his or her home is significantly associated with a 3.60% increase in hospital admission for ischemic heart disease (IHD) for those with a secondary diagnosis of congestive heart failure. Such an increase in CO is also associated with a 2.99% increase in hospital admission for IHD, with a secondary diagnosis of arrhythmia. Again, the authors attribute the health effect only to highway emissions, since CO levels rise and fall with levels of black carbon, NO_2, ultrafines, and various organic carbon constituents, based on proximity to the major roadway (Zhu et al, 2002a, 2002b). The PM mass measure in this study (PM_{10}) is never significantly associated with the health endpoints. The authors conclude that:

> This is the first epidemiologic study showing that people with IHD and accompanying CHF and/or ARR constitute a sensitive subgroup in relation to the effects of criteria air pollutants associated with motor vehicle combustion.

The level of this effect is likely understated because the study is less precise than that of Hoek et al (2002), which locates the address of the subject in relation to major roadways. Here, in contrast, CO, NO2, and PM levels to which a person was assumed to be exposed were modeled relative to the center of the zip code in which hospital admittees lived, based upon the location of the nearest two of 25 to 35 monitors in the Los Angeles area. Clearly

many of the homes would be located in areas more than several hundred feet from a major highway, while others would be very close to the highway and would have interpolated CO levels lower than those to which the location was actually exposed. Nevertheless, by beginning to relate pollution levels in the U.S. to a person's home, this study augments the study of Hoek et al (2002), again showing the positive association between a component of highway pollution (CO) and adverse health effects.

Two studies of heart disease in bridge and tunnel workers in New York (Stern et al, 1988; Herbert et al, 2000) suggest long term, chronic effects of carbon monoxide (and/or of other vehicular emissions closely associated with CO). Generally, these studies found that those workers most heavily exposed to carbon monoxide (levels were higher inside tunnels than on bridges), or exposed for longer periods (CO levels decreased markedly between the 1960s/1970s and the 1990s), had increased risks for coronary heart disease (CHD) and heart disease mortality. Stern et al (1988) reported an elevated risk of arteriosclerotic heart disease among tunnel officers, as compared with bridge officers. They also found that the risk declined after cessation of exposure, and much of the risk dissipated within as little as five years after cessation of exposure.

Herbert et al (2000) reported that CHD was strongly associated with duration of occupational exposure, with CHD prevalence increasing in a stepwise fashion with length of service. This study also catalogued a sharp decline in CO measurements inside tunnels and in toll booths (both those inside tunnels and on bridges), from a summer 1961 24-hour average of 53 ppm (inside tunnel) and a 1970 mean of 63 ppm (inside tunnel toll booth), to a 1981 mean level of 38 ppm (inside tunnel toll booth), to a 1991 range across facilities of 2.4 to 2.8 ppm (inside tunnel toll booths). These two studies did not measure PM concentrations or composition, so it may be prudent to view the results, for now, as indicative more of the effects of vehicular emissions generally. These findings, as well as the tremendous drop in CO levels over three decades, however, suggest that CO levels of previous decades likely play a role (see Toxicology section below), but perhaps not the only role, in chronic CHD effects.

Another study (Tarkiainen et al, 2003) found an association between CO concentrations and changes in short-term heart rate variability (r-MSSD) in patients with coronary artery disease, suggesting increased vagal control during the CO exposure. The study used 24-hour ambulatory electrocardiographic recording with simultaneous personal CO monitoring for the patients. The time domain measures of HRV were calculated for 5-minute segments before and during the CO exposure periods. The exposures were divided into low (< 2.7 ppm CO) and high (> 2.7 ppm CO) groups. The change in heart rate variability was found only in the higher exposure group; heart rate was unchanged. In the high CO exposure group, 23 of the 30 episodes were related to traffic, thus leaving open the possibility that traffic emissions of some type other than CO might have caused the change in HRV.

Finally, the October 2002 study of the Netherlands government (Netherlands Aerosol Program, 2002) states the following:

> "The current toxicological and human clinical evidence does not support the epidemiological observation that sulfate is a causal factor at current concentrations in the ambient air in the Netherlands. It therefore remains unclear whether or not a reduction in sulfate (as well as in nitrate) concentrations in ambient air will result in a similar reduction in health effects in the general population. *The recent results of the Dutch 7-year time-series study even suggests [sic] that lower average levels of sulfates do not necessarily lead to lower health effects in the Dutch population*." (pg. 45, emphasis ours)

Respiratory Findings

In a study of the relationship between air pollution from heavy traffic and respiratory symptoms in children, Janssen et al (2003) summarize how important it has become to be able to relate where someone lives or goes to school with proximity to roads, especially those with high traffic volume:

> "The use of geographic information systems to obtain more accurate measures of exposure to traffic-related air pollution has increased. The power of such systems was nicely illustrated by two subsequent analyses from Nottingham, the first one finding no relationship between traffic activity and wheeze in school children

> when analyzing traffic activity in the living areas in tertiles (Venn, A. et al. 2000). When the same material was analyzed for children living within short distances of major roads, a clear relationship with wheeze was observed (Venn, A. J. et al. 2001)."

The Venn et al (2001) study found that:

> "Among children living within 150 metres of a main road, the risk of wheeze increased with increasing proximity by an odds ratio (OR) of 1.08 (95% CI 1.00 to 1.16) per 30 M increment in primary schoolchildren, and 1.16 (1.02 to 1.32) in secondary schoolchildren. Most of the increased risk was localized to within 90 M of the roadside."

Large associations between vehicular emissions and asthma are reported by Nicolai et al (2003). This study finds that children living within 50 meters of a heavily traveled road were almost twice as likely to have current asthma than other children (odds ratio: 1.8). No effect modification for socioeconomic status was observed (although the authors do not rule out such a possibility). Effects decreased with greater distances from heavily traveled roads, suggesting a dose-response relationship. In addition, concentrations of three traffic-related pollutants (soot, benzene, and NO_2) were modeled, based upon measurements at 34 monitors (16 low-traffic sites, 18 high-traffic sites). Modeled estimates fit actual measurements well. The highest modeled pollutant concentrations (for all three pollutants) at each child's home were associated with asthma rates close to double those of the general population, suggesting that when highway emissions are accurately related to health outcomes, the coefficient of effect is large.

Lin et al (2002) studied childhood asthma hospitalization and residential exposure to traffic proximity and volume. Again, they found an odds ratio of almost double, for children in closest proximity to heavily trafficked roads:

> "After adjustments for age and poverty level…children hospitalized for asthma were more likely to live on roads with the highest tertile of vehicle miles traveled (VMT) (odds ratio = 1.93, CI: 1.13-3.29) within 200 m and were more likely to have trucks and trailers passing by within 200 m of their residence (odds ratio = 1.43, CI: 1.03 – 1.99) compared to controls….This study suggests that exposure to

> high volumes of traffic/trucks within 200 m of homes contributes to childhood asthma hospitalizations."

Buckeridge et al (2002) used "a refined exposure model" which included GIS systems to "demonstrate a significant effect of modeled area exposure to $PM_{2.5}$ from motor vehicle emissions on hospital rates for selected respiratory conditions." They report that such exposure:

> "…has a significant effect on admission rates for a subset of respiratory diagnoses (asthma, bronchitis, chronic obstructive pulmonary disease, pneumonia, upper respiratory tract infection), with a RR of 1.24 (95% CI, 1.05 – 1.45)."

An earlier, exploratory study, also using GIS systems (English et al, 1999), reports somewhat similar findings:

> "The results of this exploratory study suggest that higher traffic flows may be related to an increase in repeated medical visits for asthmatic children. Repeated exposure to particulate matter and other air pollutants from traffic exhaust may aggravate asthmatic symptoms in individuals already diagnosed with asthma."

A morbidity study (Brunekreef et al, 1997) also found associations between distance from major roadways and health effects. The authors found that:

> "Lung function was associated with truck traffic density but had a lesser association with automobile traffic density. The association was stronger in children living closest (< 300 meters) to the motorways. Lung function was also associated with the concentration of black smoke, measured inside the schools, as a proxy for diesel exhaust particles."

Similarly, another study (van Vliet et al, 1997) finds significant morbidity associations for living within 100 meters of the freeway (for asthma diagnosis and other respiratory symptoms) and for concentration of black smoke measured in schools and for truck traffic intensity (for chronic respiratory symptoms).

Also, Janssen, et al (2003) conclude:

> "Respiratory symptoms were increased near motorways with high truck but not high car traffic counts. They were also related to those air pollutants that were increased near motorways with high truck traffic counts. Lung function and BHR were not related to pollution. Sensitization to pollen was increased in relation to truck but not car traffic counts. The relation between symptoms and measures of exposure to (truck) traffic-related air pollution were almost entirely restricted to children with bronchial hyper responsiveness and/or sensitization to common allergens, indicating that these are a sensitive subgroup among all children for these effects."

The recent overview study of PM health effects prepared by the Netherlands Government (Netherlands Aerosol Programme, 2002) suggests that vehicle-derived PM is most likely to cause adverse human health effects, and is the type of PM to be controlled to minimize human health impacts. The report concludes that:

> "PM is a complex mixture containing fractions that are to a greater or lesser extent health-relevant….Further source-oriented actions could focus on reduction of the total PM_{10} aerosol mass or, first of all, on those PM fractions that are expected to be more health relevant. This last option is preferred. These fractions are probably transport related (diesel soot) and, more generally, combustion related primary PM emissions."

Birth Outcomes and Proximity to Highways

Wilhelm and Ritz (2003) explore the effect of proximity to major highways on adverse birth outcomes (low birth weight and/or pre-term birth) in the Los Angeles area. The authors "estimated exposure to traffic-related air pollution using a distance-weighted traffic density (DWTD) measure…[which] takes into account residential proximity to and level of traffic on roadways surrounding homes." Wilhelm and Ritz (2003) report:

> "…we find elevated risks primarily for women whose third trimester fell during fall/winter months (OR [odds ratio] $_{\text{term low birth weight}}$ = 1.39 95% CI, 1.16 – 1.67; OR $_{\text{pre-term and low birth weight}}$ = 1.24, 95% CI =1.03 –1.48; RR $_{\text{all pre-term}}$ = 1.15, 95% CI = 1.05 – 1.26), and exposure-response relations were stronger for all outcomes. This result is consistent with elevated pollution in proximity to sources during more stagnant air conditions present in winter months. Our previous research and these latest results suggest exposure to traffic-related pollutants may be important."

Toxicology of Vehicular Emissions

Because epidemiology has not been able to clearly identify which particular constituents of $PM_{2.5}$ (or associated gaseous pollutants) may most likely to be causally linked with premature mortality, scientists have called for the use of toxicology to identify the biological mechanisms by which $PM_{2.5}$ constituents might cause mortality (National Research Council, 1998; Ware, 2000).

Identification of such mechanisms would, in the process, also point to the particular constituents involved. Such identification is important for interpreting statistical associations of past years – because some vehicular emissions have already been reduced by over an order of magnitude. Identification is also important going forward, because the reduction of some pollutants in the past 25 years may reveal more subtle effects of remaining ones. This section will review toxicological findings regarding various constituents of vehicular emissions, including carbon monoxide, diesel emissions generally, and ultrafines.

Carbon Monoxide (CO)

CO is highly correlated with highway $PM_{2.5}$ emissions, as noted above, and thus potentially may be responsible for a portion of the adverse health effects attributed to vehicle-derived $PM_{2.5}$ or traffic emissions generally. Although there has been relatively little toxicological assessment of possible chronic cardiopulmonary effects of CO, one recent study (Thom et al, 1999) showed that rats exposed to 50 ppm CO for one hour developed increased capillary permeability and enhanced low density lipoprotein (LDL) oxidation.

The authors suggested that due to oxidative stress, the results offer the first biochemical mechanism that may explain an association between atherosclerosis and chronic CO exposure. It should be noted that commuters on major urban arterials typically were exposed to CO concentrations of 10 ppm as late as the mid-1990s, and in winter, peak concentration on such highways of over 20 ppm (Ott et al, 1994). In the 1970s, CO levels

inside cars were often over 100 ppm (Anderson el al, 1973). The effects in rodents (Thom et al, 1999) thus occurred at levels below those typical for human exposure in the 1970s, and at an average multiple of only 5 times urban arterial highway CO concentrations in the mid-1990s. Further, the authors did not assess whether CO concentrations lower than 50 ppm might cause similar effects.

Given how high CO levels apparently were near highways, until recently, and given the possibility of chronic atherosclerotic effects described by Thom et al (1999), it would seem reasonable that continual CO exposure on or near major roadways may have been an important contributing factor in long-term, chronic pollution effects.

In contrast, many other toxicological studies of $PM_{2.5}$ and its constituents evaluated health effects using concentrations thousands of times greater than ambient levels. Thus, in epidemiological studies of chronic cardiopulmonary effects of PM, it is possible that a large portion of any mortality related to traffic emissions might be caused by long-term exposure to CO.

In addition, because those with congestive heart failure (CHF) have difficulty getting adequate amounts of oxygen, it is possible that 10 to 20 ppm of CO could induce heart failure in those with advanced CHF. For instance, in a study of angina in human subjects, Anderson et al (1973) found that exposure to 50 ppm CO for four hours a day for five consecutive days increased carboxyhemoglobin levels from 1.3% to 2.9%, and the mean duration of exercise before onset of pain was significantly shortened. Electrocardiograms recorded during and after exercise generally 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.

Anderson et al (1973) point out that in the early 1970s, CO levels were far higher than they are today. The average CO concentration inside an automobile was found to be ~ 115 ppm in heavy traffic; ~ 80 ppm on expressways; and ~ 40 ppm in off-street, central urban areas

(eight hour averages). The authors report that mean carboxyhemoglobin levels in their study subjects, after exposure to 100 ppm CO for 4 hours, were less than those in subjects in another study who were exposed to traffic emissions for 90 minutes of heavy freeway travel. Thus an important aspect of this study is that significant acute health effects in humans, not rodents, can be found at levels similar to those many humans routinely experienced.

A later study with 63 subjects (Allred et al, 1989; Allred et al, 1991) confirms the results of Anderson et al (1973) by demonstrating a dose-dependent, statistically significant decrease in the time to ST-segment changes and to onset of angina, at somewhat higher levels of CO (CO levels of 117 and 253 ppm, resulting in carboxyhemoglobin levels of 2.0% and 3.9%, respectively).

Burnett et al (1998) discuss the toxicology of CO in assessing their finding that CO appeared to be associated with a large majority of excess deaths in Toronto from 1980 to 1994. The study (included in the CD) suggests additional ways that CO could increase mortality risks:

> "Epidemiological data indicate a potent and pervasive effect of even low ambient CO levels. Evidence obtained over the past few years on the pharmacological action of CO and its role in the CO-NO-cGMP signaling pathway suggest a role in homeostasis….Sensitive individuals may be those with precarious homeostasis, already afflicted with a pathology, and in which inhaled CO may interfere with critical functions of the immune, cardiovascular, pulmonary, and central nervous systems."

Mott et al (2002) report that unintentional motor vehicle-related CO mortality declined by a factor of 4 from 1975 (when the catalytic converter was introduced) to 1998, and that this reduction closely tracked the reduction in CO emissions per vehicle-mile. These are deaths in which the death certificate directly implicated the involvement of CO or motor vehicle exhaust (CO being the only acutely fatal compound in vehicle exhaust) in the death, and would not include any cardiopulmonary deaths unless the coroner specifically implicated CO or vehicle exhaust (Mott, personal communication); in many of these deaths,

carboxyhemoglobin levels would have been cited. The study calculates that without the reduction in CO, an additional 11,000 unintentional motor vehicle related deaths directly attributable to CO would have occurred in the time period.

By demonstrating both that vehicular CO levels have declined, and that direct CO-related mortality has declined as a result, Mott et al's results suggest that non-accidental mortality from CO-related cardiopulmonary causes, where the coroner did not directly implicate CO as a cause of death, also likely decreased in the post-1975 time frame. The findings of Mott et al (2002) thus reinforce both the toxicological findings directly above and the epidemiological findings of studies of bridge and tunnel workers (Stern et al, 1988; Herbert et al, 2000) and of CO associations with mortality in Canadian cities (Burnett et al, 1998), where the authors link CO with cardiopulmonary mortality.

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

Ultrafine Particles (UFs) and Diesel Exhaust Particles (DEP)

The role of vehicular emissions that are highly associated with CO -- such as UFs, semi-volatile organic compounds (SVOCs), DEP, black carbon, and various other carbonaceous components such as EC and OC -- should also be more fully explored, to understand the role they may play in premature mortality via cardiopulmonary effects. UF particles (those < 100 nanometers in diameter, or 0.1 μg) are created in various combustion processes, but rapidly agglomerate into "accumulation mode" particles. Because of the ubiquity of vehicular traffic, most ambient outdoor UFs that people breathe are likely to be from vehicles. Traffic-derived UFs are likely to consist of complex carbonaceous species, including condensed (SVOCs), which increase in number in cooler temperatures.

In the last three years there have been substantial numbers of *in vitro* studies to investigate the toxicity of such particles, especially DEP and UFs.

Two of these (Hiura et al, 1999; Hiura et al, 2000) show that DEP induces apoptosis in pulmonary alveolar macrophages by producing reactive oxygen species (ROS), which harm mitochondria. The researchers note that carbon black (as a control) does not produce these effects, which they suggest are due to unburnt petrochemicals in the DEP.

Li et al (2002a) show that DEP causes oxidative stress, interleukin-8 (IL-8) production, and cytotoxicity with increasing concentrations of DEP in bronchial epithelial cells, such that exposed epithelial cells produce more superoxide radicals and are more susceptible to cytotoxic effects than macrophages. Again, cytotoxicity was found to be the result of mitochondrial damage.

Li et al (2002b) then showed that organic DEP extracts induced a stratified oxidative stress response -- e.g., greater oxidative damage at higher DEP levels -- in two lines of macrophages, leading ultimately to apoptosis, as in Li et al (2002a). This study also studied the effects in these cells of concentrated ambient particles (CAPs) collected from nearby a major highway. (CAPs are PM collected in the ambient air and then concentrated to a multiple of ambient levels, usually 10 to 30 times the ambient concentration.) 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 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 DEP in inducing apoptosis, suggesting the possibility that the non-DEP portions of fine and coarse PM may be relatively innocuous, for these health endpoints.

Finally, the authors tie the oxidative stress reaction (via expression of heme oxygenase 1, or HO-1, which produces the antioxidant bilirubin intracellularly; this expression occurred as a reaction to all levels of DEP tested in this study) to possibly helping define a human subgroup that might be more susceptible to DEP. The authors point out that male smokers with a poorly responsive HO-1 promoter have a higher rate of emphysema than male smokers with a more inducible HO-1 gene. An implication is that DEP might be involved in the etiology of emphysema in individuals with a less functional HO-1 gene.

The two most recent *in vitro* studies reviewed here extend the inquiry from DEP to submicrometer and ultrafine vehicular emissions. Li et al (2003) report that (a) ultrafine CAPs from the LA basin are more potent than fine or coarse CAPs in inducing oxidative stress via generation of reactive oxygen species (ROS), including via expression of HO-1, and (b) that electron microscopy showed that UF penetrated into subcellular structures and damaged mitochondria (fine particles showed these effects to a lesser degree). The HO-1 expression was directly correlated with the high organic carbon and PAH content of UF. These findings suggest that the findings of Hiura et al (1999, 2000) above may have been due to the UF portion of DEP.

Huang et al (2003) examined the cellular effects of $PM_{1.0}$, $PM_{1.0\text{-}2.5}$, and $PM_{2.5\text{-}10}$ collected with a trichotomous impactor in Taiwan. $PM_{1.0}$ resulted in significantly higher IL-8 production and lipid peroxidation than $PM_{2.5\text{-}10}$, whereas the responses elicited by $PM_{1.0\text{-}2.5}$ were not significantly higher than blank filters. These submicrometer particles also stimulated more tumor necrosis factor (TNF-*a*) 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 of $PM_{1.0}$: IL-8 correlated with Cr and Mn, and TNF-*a* correlated with Fe and Cr. Lipid peroxidation in BEAS-2B [bronchial epithelial] cells correlated with both elemental and organic carbon content.

For each of these biological endpoints (IL-8, TNF-*a*, and lipid peroxidation), there was no correlation with sulfate concentrations.

This study, conducted in a country with a somewhat different mix of PM components, appears to generally confirm the findings of Li et al (2003) that the smaller particles ($PM_{1.0}$ in this case) are the most toxic; that markers of oxidative stress are present; and that organic and elemental carbon are important. Li et al (2003) didn't examine the possible role of metals in these responses, so the findings with regard to metals reported by Huang et al (2003) are not necessarily contradictory to those of Li et al (2003). Of particular interest is that the $PM_{1.0\text{-}2.5}$ fraction is the least toxic of the three size fractions, again suggesting the greater toxicity of the submicron and/or UF fractions.

Results of cellular studies do not necessarily predict what will happen when humans are exposed to ambient pollution. However, the findings of the studies just reviewed importantly suggest that for some health endpoints, the UF fraction of vehicular PM emissions may be the most toxic component, perhaps primarily because UF particles can penetrate cell walls more easily than larger ones.

Finally, several types of vehicular emissions, including diesel exhaust and benzene, have been identifies as potentially carcinogenic by EPA and others (U.S. EPA, 2002).

Why Omission of Studies of Highway Proximity and Health Outcomes is Important

Studies of associations with air pollution and health endpoints can be divided into short-term and long-term (primarily cohort) studies. There are far more short-term studies (e.g., those associating daily pollution with daily health outcomes), and these will be addressed in the next section. Due to the recent GAM software problems with the NMMAPS study, the HEI made the following statement in its May, 2003 "Revised Analyses of Time-Series Studies of Air Pollution and Health":

> "Some have noted that the calculated health impact of short-term air pollution based on time-series studies is substantially smaller than that of long-term air pollution based on cohort studies. Because of the vastly larger number of time-series studies performed, however, assessors of health risk from air pollution *have often had more*

> *confidence in time-series results than in results from the few cohort studies*. The problem with applying GAMs has involved primarily the time-series studies, however, and correction of the problem has generally decrease estimates of effect from these studies. *Thus, more emphasis on cohort studies can be expected*. Further, uncertainty regarding the estimates of effect obtained from time-series studies can also be expected to place additional emphasis on long-term air pollution studies, on studies of natural experiments (so-called quasi-experimental studies), and on human and animal experimental studies." (emphasis ours, study included in CD)

The CD, on pg. 8-105, makes clear its dependence, in analyzing long-term effects, on just two of the few such studies, the Six Cites and ACS studies (both of which, along with the HEI [Krewski et al, 2000] reanalyses of them, are included in the CD):

> "The lack of consistent findings in the AHSMOG study and negative results of the VA study, do not negate the findings of the Six Cities and ACS studies: the ACS studies had a substantially larger study population, and both the Six Cities and ACS studies were based on measured PM data (in contrast with AHSMOG estimates based on TSP or visibility measurements) and have been validated through exhaustive reanalysis. The results of these studies, including the reanalyses results for the Six Cities and ACS studies and the results of the ACS study extension, provide substantial evidence for positive associations between long-term ambient PM (especially fine PM) exposure and mortality."

We will address the Six Cities study further below. Here, we examine the ACS study, specifically the ACS study extension (Pope et al, 2002), in light of the highway proximity mortality findings of the Hoek et al (2002) cohort study and the toxicology of vehicular emissions, mainly CO emissions in the past two to three decades, when CO emissions were much higher, were a risk factor for both acute and chronic mortality, and were highly correlated with vehicular emissions of $PM_{2.5}$.

<u>The ACS Study Extension</u>

The ACS study extension (Pope et al, 2002), using pollution data for 151 cities from 1980 and later, finds that $PM_{2.5}$ is associated with a relative risk of 1.06 for cardiopulmonary mortality for a 10 $\mu g/m^3$ increase in annual $PM_{2.5}$ concentrations (see Figure 3 below, which is Fig. 4 from Pope et al, 2002 -- see row B, "all combined" column). The 10 $\mu g/m^3$

increase is approximately the difference in $PM_{2.5}$ levels between a relatively clean medium-sized city and a relatively dirty large one.

Also in Figure 3 from Pope et al (2002), in the column distinguishing the statistical associations with $PM_{2.5}$ among the three different education levels (less than high school, high school, and greater than high school education), Pope et al (2002) report that relative risks (RR) for cardiopulmonary mortality and for lung cancer mortality for those in the two lower education levels are both relatively large and significant; however, the RR for those with better than high school education are virtually zero and very far from significance. Similarly, the RR for all-cause mortality, for those with better than a high school education, is effectively zero, while the RRs are significant for the lower educational groups (RR = about 1.10 and 1.05, respectively).[6]

If one assumes that most PM has about the same toxicity for causing lung cancer and cardiopulmonary mortality, why is it that such risks are virtually zero for those with higher socioeconomic status (there is a high correlation between education level and income/wealth)? Alternatively, could the different socioeconomic groups be exposed to different types of pollution, with the more dangerous type(s) affecting those of lower socioeconomic status (SES)?

A recent study (Reynolds et al, 2001) evaluated the relationship between income and proximity to vehicular traffic in San Diego County. It showed that those earning < $18 K annually had average daily traffic (ADT) counts of about 50,000 vehicles within 165 meters of their home. In contrast, those with incomes between $18 K and $56 K had ADT counts of about 25,000 vehicles, and those earning > $56 K had ADT counts averaging about 8,000 vehicles. These differences were statistically significant ($P < 0.0001$).

[6] The CD understates the finding of virtually zero effect for those three health endpoints, for those with better than high school education: it merely notes (pg. 8-84) that "the association between an increase in fine particles and mortality tended to be higher for individuals without a high school education than for those with more education."

Another study showed that individuals with lower SES are exposed to higher levels of PM (Jerrett et al, 2001). The EPA Trends Report (U.S. Environmental Protection Agency Trends Report, 2001) showed that urban $PM_{2.5}$ concentrations are approximately twice as high as rural concentrations in the eastern U.S. Another study (Hansen et al, 2003) finds that most of the difference in PM mass between rural areas such as Centreville, AL and urban areas such as Atlanta, GA can be explained by increases in concentrations of organics, which would be due largely to vehicular emissions in cities. Taken as a whole, these studies suggest that those with lower SES are exposed to considerably more vehicular emissions and also to higher PM levels, and that these higher exposures to both tend to occur in urban areas.

Regional pollution is itself influenced by traffic sources in large metropolitan areas. For example, in large urban areas there are generally more congested highways with more traffic than in smaller localities, and measures of regional air pollution (e.g. PM_{10}, $PM_{2.5}$, and sulfates) are generally higher because local PM emissions, much of them from traffic, are added to regional concentrations of all three.

We suggest that the reason those with higher socioeconomic status in ACS reanalysis are apparently immune to the health effects of $PM_{2.5}$ is that such people on average are not exposed to nearly as much highway pollution (Jerrett et al, 2001; Reynolds et al, 2001).

The alternative hypothesis is that those with higher educational levels are exposed to pollutants that are equally likely to cause cardiopulmonary or lung cancer mortality as are those with less education, but that a combination of better access to health care, more attention to personal fitness and health, and better diets completely negates the health threat. Clearly, better educated people will benefit from these advantages, but can these advantages bring their risk to zero for an elevated RR for both cardiopulmonary and lung cancer, if all types of $PM_{2.5}$ have roughly the same potential to cause these outcomes?

Cardiopulmonary risks should be reduced by higher socioeconomic status, given that those in health care plans, and with better physician care, would seem to be more likely to be on

statin drugs, if appropriate. But it seems unlikely that such risks could be brought to zero, if $PM_{2.5}$ exposure were the causal factor, and if all $PM_{2.5}$ were equally toxic.

Lung cancer risks would appear to clarify this point further. Until recently, those with lung cancer could not expect to have their lives extended by more than a few months to the better part of a year, on average, even with chemotherapy. The ACS study started enrollment in 1982, and the ACS reanalysis used mortality figures through December 31, 1998. Most lung cancer deaths would therefore have occurred before the recent modest improvements in longevity for lung cancer. It seems quite clear that an RR for lung cancer mortality would not be much lower for the better educated, and certainly could not have become zero.

Thus, in choosing between two alternative theories for why the better educated seem to have no increased RR for either cardiopulmonary or lung cancer mortality in the ACS reanalysis -- one that suggests that better availability of health care and better attention to health will completely negate the risk from $PM_{2.5}$ (implicitly assuming all $PM_{2.5}$ is toxic enough to increase mortality risks for these diseases), or another interpretation which suggests, based upon the studies noted above, that those with lower education are exposed to much more vehicular emissions where they live[7], and that toxicological evidence supports the idea that these emissions could cause those with less education to have higher RRs for both adverse cardiopulmonary and lung cancer outcomes -- the second theory, suggesting higher exposure to vehicular emissions, seems more likely.

But those with higher education, even if they would have tended to live proportionally more in suburbs in the 1980s and 1990s, are still exposed to $PM_{2.5}$. What is the nature of such pollution, if it contains sharply less vehicular emissions (Reynolds et al, 2001)?

[7] Suburban commuters or urban dwellers living farther from major urban roads would be exposed to vehicular emissions during commuting, but the hours per day of exposure would be considerable less than for those living in close proximity to major urban roads and thruways.

In the eastern U.S., ambient secondary sulfate and nitrate, as well as various organics, are almost ubiquitous, and thus virtually all residents would be exposed to them. Is there any evidence addressing the toxicology of these pollutants?

Schlesinger and Cassee (2003), in a 37 page overview article (not included in the CD) examining approximately 150 toxicological studies to date of the effects of secondary sulfates and nitrates, report 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 which will require additional research. This study is in contrast to the CD on pg. 9-55 (in the Integrative Synthesis section):

> "The epidemiologic results suggest the need for toxicological studies of the sulfate, nitrate, and organic components of PM, including studies with compromised or susceptible individuals."

We agree that more toxicology is needed – one example would be for the types of organics possibly affected by acid catalysis (should acid catalysis prove to be an important factor), both before and after catalysis, in order to see whether putative catalysis makes organics more toxic or less toxic, or to find if they are toxic in either formulation (see discussion immediately below).

However, it is important to point out that there is already a large body of toxicological studies on *secondary* sulfates and nitrates. Later in our comments, we draw a distinction between secondary sulfates and primate vanadium and nickel sulfate emissions (in ROFA) from residual oil-fired power plants.

Recently, laboratory studies have suggested that SO_2 emissions, as they are oxidized in the atmosphere first to very dilute H_2SO_4, and then to ammonium sulfate and ammonium bisulfate, might catalyze various atmospheric organic compounds into larger organic

molecules. The toxicity of these organics at relevant ambient concentrations, either before or after catalysis, isn't currently known. Thus neither of these groups of $PM_{2.5}$ species might be toxic at ambient concentrations; both might be toxic; or perhaps the only toxic groups are those prior to any catalysis, or those after such catalysis. However, to the extent that such catalysis occurs in the atmosphere as well as the laboratory, better educated people would be exposed to them, and the findings of the ACS reanalysis thus appear to suggest that there would be no harm from them (approximately zero RR for total mortality, cardiopulmonary mortality, or lung cancer, for those with better than a high school education).

The suggestions in this section – e.g., that vehicular emissions are likely to be among the more harmful fractions of contemporary air pollution, and that regional emissions such as secondary sulfates and nitrates, as well as other emissions highly correlated with them are likely to be no more than negligibly harmful -- are buttressed by those of four studies found in the CD: Janssen et al (2002), Metzger et al (2003), Creason et al (2001), and Friedman et al (2001).

Janssen et al (2002) Study

Janssen et al (2002) broke new ground by exploring how the prevalence of air conditioning (AC) might affect the associations of outdoor PM exposure with health outcomes. With central air conditioning, air exchanges with outdoor air are usually minimized, thus reducing exposures to pollutants of ambient origin. Use of AC as an effects modifier does in fact appear to adjust and clarify statistical associations.

Janssen et al (2002) report that hospital admissions for cardiovascular disease increased significantly with increased exposure to 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, as a check on their findings regarding emissions from highway vehicles/diesels. VMT was highly correlated with the

highway emission variables, and also yielded a statistically significant positive association with hospital admissions for cardiovascular disease.

Janssen et al (2002) is mentioned several times in the CD, among several discussions where the CD notes the potential importance of vehicular emissions. For example, on page 8-111, the CD states:

> "Two of the ecological variables, vehicle miles of travel per square mile per year by gasoline (VMTG) and diesel (VMTD) vehicles, respectively, in a county (also used in Janssen et al, 2002) are likely to have important associations with air pollution."

Also, on pg. 8-126, the DC notes additional Janssen et al (2002) findings:

> "…separate analysis for nonwinter-peaking and winter-peaking PM_{10} cities yielded coefficients for CVD-related hospital admissions that decreased significantly with increased percentage of central AC for both groups of cities. There were also significant positive relationships between CVD effects and PM_{10} percent emissions from highways or from diesel vehicles, suggesting that mobile source particles may have more potent cardiovascular effects than other particle types."

The CD accurately reports that Janssen et al (2002) found associations both with vehicular emissions, but perhaps more importantly, with VMT per square mile, which should show intensity of vehicular traffic more accurately than emissions levels determined from one or more area monitors.

Two points are worthy of mention here.

First, the CD explicitly recognizes the possibility that mobile source emissions might have more important cardiovascular effects that other particle types. Why, then, would the CD not include or consider precisely those studies which relate proximity to emissions from busy roadways to health effects, especially for mortality, and why would they not explore the implications these studies may have for pollution control under the NAAQS?

Secondly, because CO is so highly correlated with highway PM and ultrafine emissions (and presumably with other emissions, such as SVOCs and PAHs as well), we need to

again recognize that the effects found in Janssen et al (2002) and cited by the CD above, could largely be due to CO instead of PM, at least in the historical period of from two to three decades ago through the mid-1990s. In that time frame, CO levels on and adjacent to busy highways were above levels found to cause LDL oxidation and the basis for atherosclerotic plaque in rodents (Thom et al, 1999), and above levels which caused increasing angina pain and worsening of ST segment changes in the heartbeat, with earlier onset and longer duration of ST segment depression, as CO levels increased from 50 ppm to 100 ppm (Anderson et al, 1973). We have yet to unearth any toxicological studies which suggest any other component of vehicular emissions could have this kind of effect on any type of heart disease at ambient levels of the emission.

However, we could find no mention in the CD that Janssen et al (2002) never finds a significant association with coal plant emissions (virtually all secondary sulfates), nor that the coefficients for coal emissions are virtually zero. Nor could we find mention in the CD that the researchers found a significant association between health outcomes and residual oil emissions:

> "PM_{10} coefficients for CVD increased significantly with increasing percentage of PM_{10} emissions from highway vehicles, highway diesels, oil combustion, metal processing, decreasing percentage of PM_{10} emissions from fugitive dust, and increasing population density and VMT/mile[2]. *In multivariate analysis, only percentage of PM_{10} from highway vehicles/diesels and oil combustion remained significant*." (from Janssen et al abstract, emphasis ours)

The CD would thus be improved if the additional findings of Janssen et al (2002) with regard to both coal emissions and residual oil emissions were included.

Metzger et al (2003) study, in press

The CD makes note of some of the findings of this study, e.g., that in single-pollutant GLM analyses, CVD was associated with $PM_{2.5}$, organic carbon, elemental carbon, oxygenated hydrocarbons, CO, and NO_2 (pg. 8-129). Other findings of the study are also relevant for EPA and CASAC consideration:

(1) "In multi-pollutant models, the estimates for NO_2 remained elevated during the seven-year [1993-0222] period, while CO estimates were elevated during the 25-month period. These two pollutants are strongly correlated." Thus, for both time periods studied, only a gaseous emission associated with vehicular emissions remained positive and significant.
(2) In a five pollutant model for the 25-month time period, only CO had a positive, significant association, e.g., a RR of 1.065 per standard deviation.
(3) 24-hour water-soluble metal $PM_{2.5}$, 24-hour sulfate $PM_{2.5}$, and 24-hour acidity $PM_{2.5}$ were never significantly associated with any of the morbidity measures.

Thus the Metzger et al (2003) study offers confirmation of the results of Janssen, et al (2002) with regard to reported findings both for vehicular emissions and for emissions from coal usage. It should be pointed out that both these studies are advances in earlier epidemiological studies, but for different reasons. Janssen et al (2002) pioneers the use of air conditioning as a modifier, while Metzger et al (2003) are among the Atlanta area studies which monitor far more variables than previous studies.

Creason et al (2001) Study

Creason et al (2001) examine heart rate variability among elderly retirees for a total of 24 days.

On just two of those days, there no heart rate variability was found. On those two days, the authors report that the wind was blowing from the NE, from rural Pennsylvania, and that the $PM_{2.5}$ levels were the highest (~ 51 $\mu g/m^3$) and third highest (~ 37 $\mu g/m^3$) of the days in the study, and that the sulfur content of the air parcels was approximately average for the 24 days as a whole, although the indoor sulfate percentage of $PM_{2.5}$ was less than average for the study on these two days. These rural air parcels thus were likely the highest in terms of sulfate content, and likely among the highest in terms of any organics that may have been catalyzed, but they are the only days, apparently, without much pollution from urban environments:

> "These 2 days were the only days with significant precipitation in combination with elevated $PM_{2.5.}$ They were also unusual in that back-trajectory of their air masses

> was distinctly different from those on the other study days, emanating from the direction of rural Pennsylvania." (Creason et al, 2001, Abstract)

The authors note that there was rain on these two days as well as on two subsequent days. The rain did not change HRV outcomes on the two other days when the air mass was not from rural Pennsylvania.

The authors note the difference in pollution types and sources:

> "These differences may indicate that fine particles on these 2 days had different sources and composition than on the other 22 study days." (Creason et al, pg. 121)

The CD comments on the Creason et al (2001) study on pg. 8-139, but with regard to the two days on which there is no heart rate variability, notes only that there was rainfall on those days, not that the composition of the $PM_{2.5}$ was different, nor that rainfall on other days did not change a finding of heart rate variability on those days.

Friedman et al (2001) Study

The CD reviews on pg. 8-155 the results of the Friedman et al (2001) study of the effects of traffic reduction on asthma events during the 1996 Summer Olympics. Both ozone (28%) and PM_{10} (16%) decreased during the Olympics, due to reduced road traffic, reduced commutes, and increased mass transit during the games. As reported in the CD, a significant reduction in asthma cases was related to the reduction in ozone, but not to the reduction in PM_{10}.

In comparison to the hundreds of studies using one or more area monitors, the interpretation of which is always difficult in the absence of better exposure information, a "with and without" study like this one appears to offer a clearer interpretation. Automotive traffic declined, auto-relative pollutants declined, and asthma cases declined – as one would expect from the several studies reviewed above demonstrating associations between asthma outcomes and proximity to highways. While we may not know for sure whether

the reduction in ozone was the reason for the reduction in asthma – presumably a number of specific chemicals in vehicular emissions were reduced as well – it seems quite likely that a reduction in vehicular emissions overall was responsible for the decline in asthma cases.

The Six Cities Study

The "Six Cities" study (Dockery et al, 1993) studies 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 and Boston) from 1978 through 1988. As noted previously, sulfate and $PM_{2.5}$ were extremely highly correlated (98%).[8]

In comparing the most polluted city (Steubenville) with the least polluted city (Portage, for $PM_{2.5}$), the authors found elevated risks for both all cause mortality and for cardiopulmonary mortality (Table 5 in Dockery et al, 1993). They also found that the crude probability of survival over 16 years among the six cities was sharply lower only in Steubenville and St. Louis (moderately lower in the other four cities – Figure 2 in Dockery et al).

After examining data on the different types of emissions in the different localities, we conclude that the Six Cities study is a good illustration of the different effects of different types of emissions.

In Steubenville proper, there were an assortment of blast furnaces, open hearth furnaces, and other hot and cold metal working facilities. About 3 miles downriver, there was over 600 acres of coking facilities, capable of making about 5,000 tons of coke per year.[9] Since

[8] Pg. 151, Table 17, in Part II: Sensitivity Analysis, Krewski et al (2000).
[9] 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.

1980, there have been federal requirements to substantially reduce coke oven emissions.[10] In addition to these facilities, there were additional steel making facilities about 3 miles upriver. Given the toxicity of pre-control coke oven emissions, and perhaps of concentrated steel making as well, it isn't any surprise that Steubenville pollution was more toxic than in most of the other cities.

St. Louis, too, had a mixture of pollution sources not typical for the U.S., with high toxicity and no longer in operation. These included a large coke facility (Carondelet Coke) and lead smelters in St. Louis proper as well as four miles north in Granite City, Illinois.

How toxic these emissions in St. Louis might be is suggested by a comparison of $PM_{2.5}$ and sulfate levels in Harriman with those in St. Louis. From Table 1 in Dockery et al (1993), Harriman and St. Louis had identical sulfate measurements (8.1 $\mu g/m^3$), and Harriman actually had slightly higher PM concentrations (20.8 vs. 19.0 $\mu g/m^3$). A 1,700 MW TVA coal-fired power plant is in close proximity to the monitor location in Harriman. Yet those in St. Louis had a far lower probability of survival than those in the Harriman area (Figure 2 in Dockery et al). We suggest it is the nature of the emissions that is related to the sharply lower probability of survival in St. Louis, in comparison to Harriman.

We also note that although Steubenville had higher $PM_{2.5}$ and sulfate levels than St. Louis, it had about the same probability of survival over 16 years, lower than the other four cities. Again, this similar probability of survival could be related to the similar nature of the more hazardous emissions, especially from pre-control coke ovens.

[10] See http://ceq.eh.doe.gov/nepa/reports/1993/chap1.htm for fuller description of toxicity of coke oven emissions, and of a negotiated reduction of about 85% to 90% of emissions, circa 1993. Extract: "**Coke Ovens.** In October 1993 the EPA issued a final rule sharply reducing emissions from coke oven batteries. Coke is used in blast furnaces for the conversion of iron ore to iron in the process of making steel; the conversion is performed in coke oven batteries. Coke oven emissions are among the most toxic of all air pollutants, with preregulation maximum individual risks of contracting cancer running as high as 1 in 100 in some cases. The EPA developed the final rule through a formal regulatory negotiation that included representatives from the steel industry, state and local agencies, environmental groups, and the Steel Workers Union. The rule will result in overall reductions of 82 to 94 percent of total emissions from coke ovens."

These points again reinforce the notion, advocated by the National Academy's National Research Council, that different types of $PM_{2.5}$ are likely to be more harmful than others, and that we need to identify the most hazardous air pollutants in order to protect the public health.

We would also observe that although others have suggested that associations in the Six Cities study and its reanalysis (Krewski et al, 2000) between sulfate levels and adverse health outcomes show that sulfate is harmful to people, the 98% correlation between sulfates and $PM_{2.5}$ in Dockery et al (1993) doesn't permit such an inference. This is because when any two variables are so highly correlated, they will both be associated with the health outcomes, even if only some portions of one of the variables may be causally related. For example, in this case, if one or more chemical types of $PM_{2.5}$ might be causally related to adverse health outcomes, then in the case of a 98% correlation, both $PM_{2.5}$ mass and sulfate will also be associated.

Short Term Studies

In addition to the quote above from the May, 2003 NMMAPS study -- which suggests that choice of model can have an important impact on the size and significance of the coefficients of effect, and which suggests that with the NMMAPS difficulties, the long-term (cohort) analyses would become more important -- we would make two other observations about short term studies.

First, although there are literally hundreds of short-term studies of the health effects of PM and other air pollutants, virtually all of these depend on just one or a few monitors in a given area, and thus may not find associations with local pollutants with high variability, except by chance. Even in that case, however, the effects may be understated, because the exposure of affected individuals may be underestimated. Not unexpectedly, these studies often come to very different conclusions about which pollutants are more significantly associated with health outcomes, with larger measures of effect. For example, while there are many short-term studies that find (highly variable) CO to be highly associated with

cardiopulmonary mortality or morbidity, others find the opposite. There is usually less variability in associations involving $PM_{2.5}$ and sulfates, because these two pollutants are more regional in nature, are highly correlated, and are higher in larger, more populated areas than in smaller ones.

Prior to the Zhu et al (2002a, 2002b) studies demonstrating extreme local variability, and the several studies in the highway proximity section above showing large adverse health impacts for those living in close proximity to major roadways, reliance on studies using one or a few area monitors was necessary. In addition, it may not have been clear that an apparent reason studies came up with conflicting results for vehicular emissions such as CO was that monitors in some studies were placed in positions near major highways, while in other studies, the monitors were placed farther away. For example, in Burnett et al (1998), one of the monitors is located 75 meters from a major Toronto freeway; perhaps unsurprisingly, the associations with CO are higher than in most short-term studies.[11]

The recent NMMAPS findings may well be a case in point. The May reanalysis pooled data from all 90 localities across the U.S., which amounts to an assumption that PM in different areas has approximately the same health impact. The "pooled" results continued to be significant, although the overall coefficient size dropped by 1/3 to 1/2, depending on whether the GAMS model continued to be used, but with stricter convergence criteria (1/3 drop), or whether other models were used (1/2 drop).

But approximately 1/3 of the localities in the new HEI report, post-GAMS statistical issues, actually have negative coefficients – that is, higher PM levels are associated with lower mortality. The two areas of the country with the highest and most dense levels of vehicular traffic would appear to be the Northeast and Southern California, and these are the two areas with the highest coefficients of effect in both the old and the new (lower) NMMAPS results. A third of seven geographical areas analyzed in NMMAPS, the Industrial

[11] Burnett at al (1998) find that of the 40 daily non-accidental deaths in metropolitan Toronto, 4.7% of them could be attributable to CO, with an additional 1.0% attributable to TSP, based on changes in CO and TSP equivalent to their average concentrations.

Midwest, also has a significant association, but the coefficient of effect is lower than for the Northeast and Southern California. There are large cities and automotive traffic in all areas of the country, which would in all likelihood cause there to be positive associations for at least a few localities in any part of the U.S., thus it isn't surprising that about 2/3 of the individual location associations are positive. It is the negative associations, and the number of them, that is surprising.

Given the results above, it would appear that heterogeneity is likely, e.g., that different localities will have different levels and significance of associations because the constituents of PM and of air pollution generally, are different. NMMAPS examined heterogeneity, and stated the following:

> "Formal tests in NMMAPS for heterogeneity of PM effect across cities did not indicate heterogeneity. The Panel recognizes, however, that the power to assess the presence of heterogeneity was low because of the generally larger city-specific standard errors. The possibility of heterogeneity therefore remains."

Given the importance of the highway proximity studies, and given that the NMMAPS study didn't have a means to take into account highway proximity, one way to consider the NMMAPS results is to think about how these results might change if, for example, VMT per square mile were included as a variable (in addition to socioeconomic variables), and if use of AC as a modifier were used as well. While such an analysis would only be an approximation of the full effects of highway proximity, it would be a step in the right direction. Until such an examination is done, it isn't clear how to interpret the NMMAPS study.[12]

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[12] DOE's comments on the 2002 CD for Particulate Matter also addressed the heterogeneity issues:

"The NMMAPS project examines the relationship between PM10 and premature mortality in 90 localities, in the 1987-1994 time period. As noted above, in the reanalysis necessitated by software issues, about 1/3 of the localities now have a negative association between premature mortality and rising PM10 levels, an increase of about 10 cities from before the reanalysis.

One of the important goals of NMMAPS was to examine "heterogeneity," e.g., why some localities had negative associations and others positive ones. Let us list some of the localities east of the Mississippi that have negative associations: Cleveland, Akron, Dayton, Grand Rapids, Fort Wayne, Buffalo, Washington

Other Selected Studies in the CD

Hundreds of studies are referenced and analyzed in the CD, but some appear to be more important that others. For example, in conferences and other public presentation, EPA personnel often refer to the study by Laden et al (2000) (included in the CD) as evidence that sulfates may be associated with premature mortality.

Before discussing the study, it is important to note differences in chemical species. Water (H_2O) and hydrogen peroxide (H_2O_2) are both simple compounds made up of just hydrogen and oxygen atoms, yet we need to drink the first, and should avoid drinking the second.

Similarly, secondary sulfates, mainly ammonium sulfate and ammonium bisulfate, appear to be benign at ambient levels (Schlesinger and Cassee, 2003), while vanadium sulfate and nickel sulfate, primary emissions from the stacks of plants burning residual oil, are more likely to be toxic (Costa and Dreher, 1997). It is important to recognize that all sulfates are not the same, either in chemical formulation or toxicity (indeed, sulfates are an integral part of several asthma medicines). Thus a statistical association that uses "sulfate" as an independent variable might be measuring compounds of different toxicity, thus making

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(DC), Norfolk, Arlington (VA), Atlanta, Orlando, Nashville, New Orleans, Raleigh, Knoxville, Jacksonville, Greensboro (NC). At least two observations can be made from this short list:

(1) Many of these localities are in the parts of the US that have the highest sulfate levels, such as Ohio, Indiana, Michigan, and western New York (go to http://nadp.sws.uiuc.edu/isopleths/ , then see sulfate PDF concentration maps for 1994-2000).
(2) None of these localities are in New England or the Atlantic coast north of Washington, even thought sulfate levels are generally relatively low in these areas, according to the isopleth maps. (In the 1987-1993 time period, sulfate levels were higher, but the isopleth maps only go back to 1994.)

These observations, of course, do not prove that sulfates cannot be part of the PM problem, but they are consistent with the conclusion that sulfates [secondary sulfates] may not contribute to adverse health effect such as premature mortality, and add to the evidence (toxicological and epidemiological) noted above. We recommend that the NMMAPS analysts explore reasons for the heterogeneity they have found, and find ways to examine the PM2.5 constituents in a set of localities with positive associations between PM10 and premature mortality, and in a set of localities with negative ones, as a start."

interpretation of findings difficult. An illustrative example is given in the next section, below.

Laden et al (2000) Study

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 the 1979-1988 period from vehicles (using lead [Pb] as a tracer element) and from coal (using selenium [Se] as a tracer). Laden et al (2000) also found that sulfur (S, measured as sulfate) was significantly associated with daily mortality in the combined analysis. For both Se and for S, Boston was the only individual city with significant associations. The coefficients of effect in Boston were much higher than in cities with higher S and Se levels, in some cases more than an order of magnitude higher (see Table 1).

Laden et al (2000) has always been a puzzling study because Boston had the lowest Se levels, and the fourth lowest S levels, of the six cities (see Table 2). With the highway proximity studies of morbidity, there is frequently a dose-response function: e.g., for those living within ~ 200 meters of a major road, the tertile with the highest numbers of vehicles within ~ 50 meters of their door have the highest morbidity coefficient and the highest significance level; the next tertile is lower for both; and the third tertile lower still.

But with Laden et al (2000), there is an approximation of the *reverse* of a dose response function.

Why would the city with the lowest ambient concentrations 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 is raised for the S factor.

A new analysis (Grahame and Hidy, 2003, in press) suggests an explanation. Using three different methods and an EPA data base for trace elements in residual oil emissions, the authors suggest that about half the very small amount of selenium found in Boston air in Laden et al (0.7 ng/m^3) comes from the 1,700 MW of residual oil plants 5 to 6 miles from the monitor in the Boston region (in Watertown, MA) and from other local residual oil burning, and about half the sulfate isn't secondary sulfate, but rather is primary vanadium and nickel sulfate from the nearly residual oil sources. The authors cite both Schlesinger and Cassee (2003) as indication that secondary sulfates and nitrates are unlikely to cause mortality at ambient levels, and Costa and Dreher (1997) to suggest 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.

The authors also hypothesize that because only one monitor is used in the Laden et al (2000) study, and that this monitor is about a mile north of a very heavily used thruway (the Massachusetts Turnpike, I-90), there is a possibility that on stagnant days when pollution and mortality are relatively higher, the monitor might not pick up much of the increase in traffic emissions (keeping in mind that pollutants in the "A frame" disperse back to near-normal levels within 300 meters), due to the distance from I-90, but might instead pick up an increase in residual oil emissions. If this were the case, then perhaps vehicular emissions would, with better assessment of individual exposure profiles, have more association with mortality, and coal or residual oil emissions less, in Boston in the 1979-1988 time frame.[13]

With this reanalysis of Laden et al (2000), the results are now consistent with those of Janssen et al (2002), e.g., that vehicular and residual oil emissions, but not secondary sulfate and nitrate emissions, are statistically associated with adverse health outcomes. The reanalysis of Grahame and Hidy (2003) also appears to be consistent with the extensive discussion above of the ACS update (Pope et al, 2002), in which better educated people,

[13] Vanadium, a tracer element for residual oil emissions in most cases, was measured at 23.2 ng/m^3 in Boston in the 1979-1988 time period of the Laden et al (2000) study. According to AIRS data, vanadium levels in Boston had fallen to 5 ng/m^3 by 2000, reflecting reduced use of residual oil by that date.

less exposed to highway emissions, but exposed to regional emissions, appear not to have increased risks for either all cause, cardiopulmonary, or lung cancer mortality.

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FIGURES

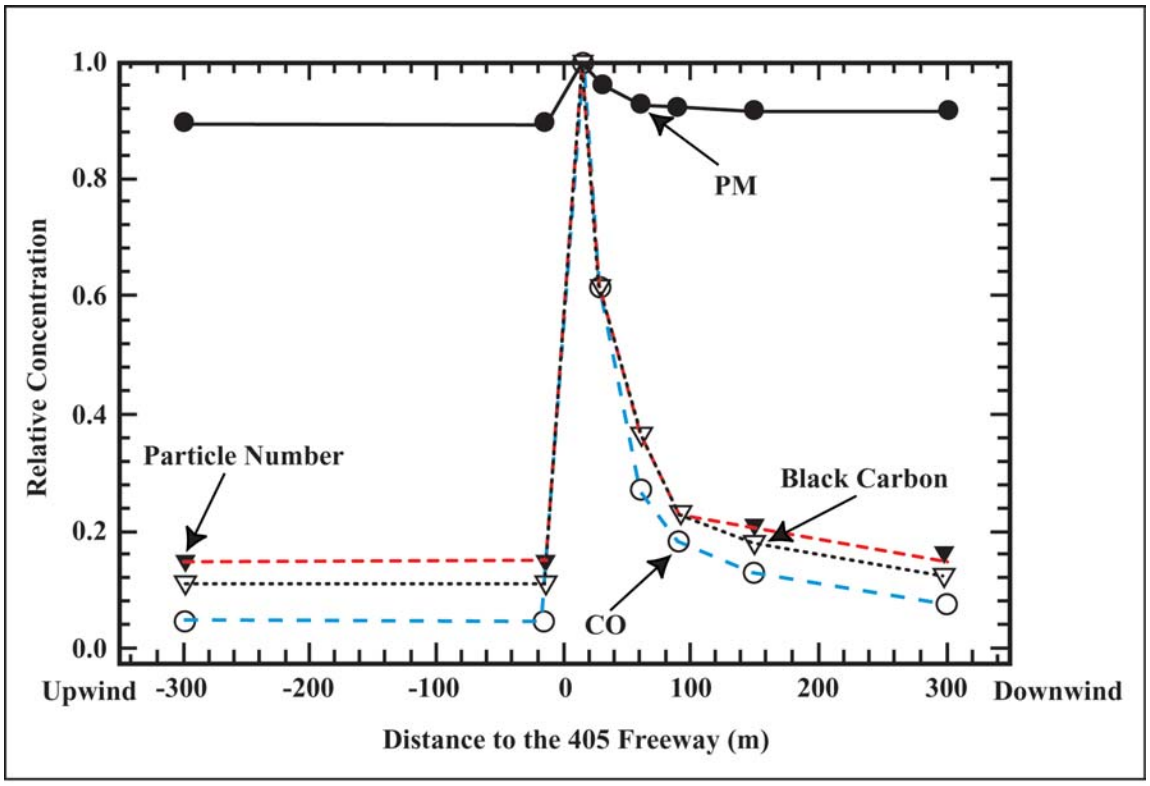

Figure 1: "A-frame" of highway pollutants (from Zhu et al, 2002a)

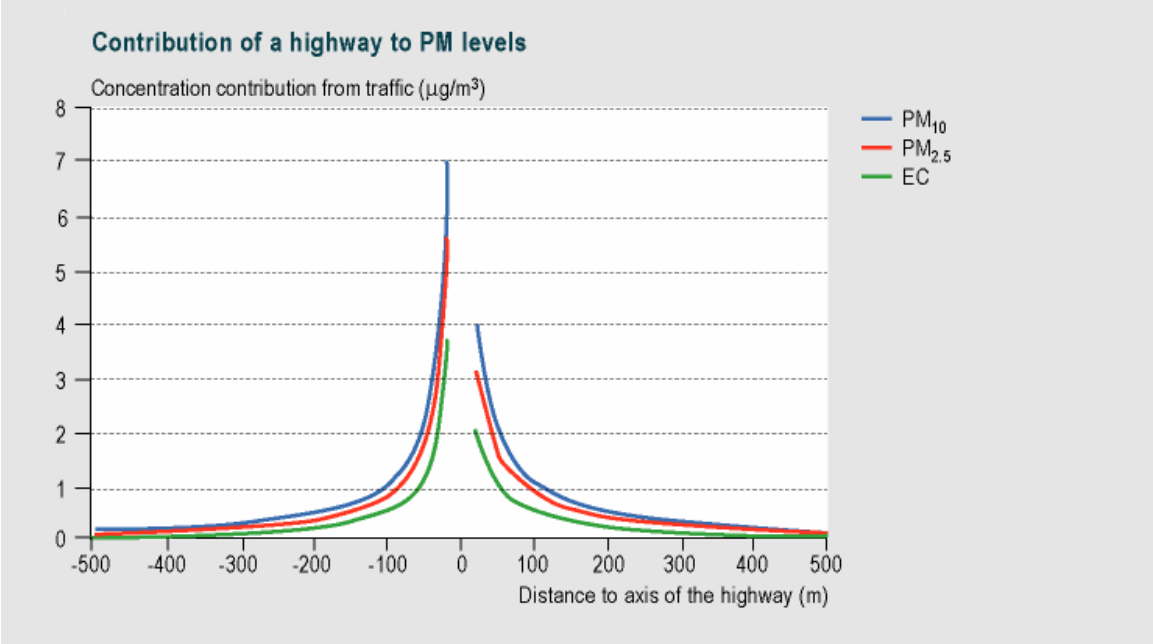

Figure 2: Relationship of distance from highway to concentrations of PM and EC (from "On Health Risks of Ambient PM in the Netherlands, Executive Summary," 2002)

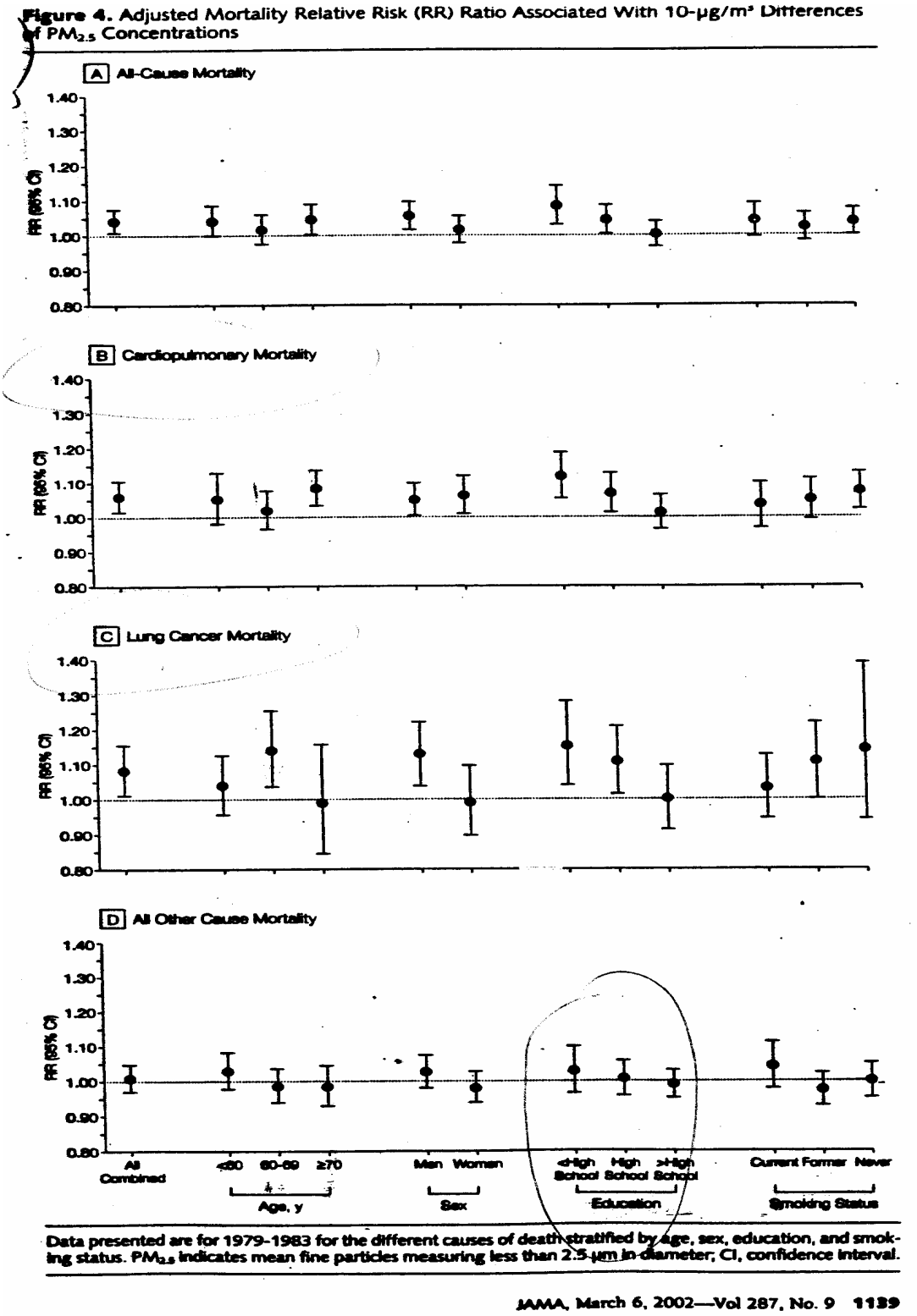

Figure 3: From Pope et al (2002), ACS Study update

Table 1. Percent Increase in Daily Deaths and 95% CIs for Se [Coal tracer] and S (from Laden, et al., 2000)[a]

	Boston	St. Louis	Knoxville	Madison	Steubenville	Topeka	Combined
Se factor	2.8% 1.2 – 4.4	0.3% -1.1 – 1.6	0.8% -2.7 – 4.3	0.9% -2.5 – 4.2	1.1% -1.2 – 3.5	-3.9% -11.2 – 3.5	1.1% 0.3 – 2.0
Sulfur	7.9% 3.9 – 12.1	0.8% -2.4 – 4.2	1.0% -6.8 – 9.4	4.6% -3.0 – 12.7	0.5% -6.8 – 8.3	-10.3% -23.1 – 4.6	3.0% 0.9 – 5.2

a. For Se, percent increase is for a 10 μg/m3 increase in mass concentration from the coal source; for S, percent increase is for an increase from the 5th to the 95th percentile.

Table 2. Levels of PM2.5 and Selected Elements in the Six Cities (from Laden, et al., 2000). Standard deviations are in parentheses.

	Boston	St. Louis	Knoxville	Madison	Steubenville	Topeka
PM2.5 (μg/m^3)	16.5 (9.2)	19.2 (10.1)	21.1 (9.3)	11.3 (7.5)	30.5 (22.4)	12.2 (7.1)
Sulfur (ng/m^3)	1922 (1392)	2350 (1583)	2556 (1491)	1482 (1327)	4248 (3185)	1368 (1169)
Selenium (ng/m^3)	0.7 (0.9)	2.2 (1.9)	1.9 (1.5)	0.9 (0.8)	5.2 (4.2)	0.8 (0.7)
Vanadium (ng/m^3)	23.2 (19.8)	2.0 (4.4)	1.4 (3.3)	0.1 (2.9)	10.5 (20.4)	0.6 (2.8)
Iron (ng/m^3)	62.2 (53.5)	143.7 (132.7)	116.9 (89.1)	44.1 (45.7)	542.2 (738.3)	72.0 (88.2)