Alliance of Automobile Manufacturers
Comments on the
U. S. EPA's First External Review Draft of the
Policy Assessment for Particulate Matter

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Executive Summary

Based on a review of the First External Review Draft of the Policy Assessment for Particulate Matter (PA), a number of changes need to be made to assure that the document accurately reflects the latest scientific knowledge concerning the health effects of fine and coarse PM. The most important of these are as follows:

- Since PM is a mixture of many different substances that have vastly different underlying toxicities, the PA must acknowledge:
  - There are unusually large uncertainties involved in setting PM standards.
  - The assumption that all fine PM can be treated as equally toxic is scientifically unsound.
  - Any conclusions regarding causality in the current review should refer to "PM (or one or more PM component) acting alone and/or in combination with gaseous pollutants" as likely causing health effects rather than to PM mass alone.
- As discussed in detail in the body of these comments, the data are not as strong or consistent as portrayed in the draft PA. The pattern of associations in multi-city studies is not consistent with an effect of generic $PM_{2.5}$ mass.
  - There is great stochastic variation in individual-city associations, with an unrealistic range of positive to negative associations.
  - There is a spatial and temporal pattern in the combined associations with little or no association in significant portions of the country and during a significant portion of the year.
  - A similar spatial pattern is found in acute morbidity and mortality as well as in chronic mortality studies.

- The PA must acknowledge these patterns in the data that are documented in the ISA as well as conclude that relying on specific single-city studies in light of the stochastic variation is unsound.

- Model selection uncertainty is a much larger issue than acknowledged in the draft PA.

  - A new study focusing on the model selection issue using 20 years of data from 12 Canadian cities suggests that the epidemiological evidence relied on by EPA in the ISA is scientifically unsound and should not be used as a reason to lower the present PM NAAQS.

  - The pattern of associations in a recently-released comprehensive study sponsored by the Health Effects Institute is not consistent with what one would expect if PM health effect associations have a real physiological basis. While there are positive and significant combined associations for some models and for some endpoints and for some geographic areas, the overall pattern of associations in the large APHENA study is mixed and inconsistent.

- The PA should include a comparison of the fine PM risks it assumes with the PM risks from other exposure situations.

  - The cardiovascular health signal relied upon by EPA is not coherent with fine PM risks from indoor pollution in developed countries, indoor pollution in underdeveloped countries, smoking, and occupational exposures.

As a result of these problems with the draft PA, the discussion of the adequacy of the current fine PM standards is flawed and the preliminary recommendations for revising the standards, since they are based on biased evaluations of the data, are also flawed.

With regard to coarse PM, we agree with EPA that urban and rural coarse thoracic PM should be treated equally. Due to the many uncertainties outlined in these comments, EPA should focus on identifying the toxic components of ambient PM. Tightening the generic fine or coarse PM standards without knowing what causes the variations in PM associations from positive to negative, at the same PM exposure, is scientifically unsound.

Introduction

The U. S Environmental Protection Agency (EPA) is in the process of reviewing the National Ambient Air Quality Standards (NAAQS) for particulate matter (PM). The Integrated Science Assessment for Particulate Matter[1] (ISA), which reviews the relevant science, was completed in December 2009. As part of the review, EPA has issued the

[1] U. S. Environmental Protection Agency, Integrated Science Assessment for Particulate Matter, EPA/600/R-08/139F, December 2009.

first draft Policy Assessment[2] (PA) that is intended to help "bridge the gap" between the relevant scientific information and the judgments required of the Administrator in determining whether, and if so, how, it is appropriate to revise the standards. AIR, Inc. reviewed the draft PA, focusing on the way the relevant science is interpreted in the document and how that information bears on the question of the adequacy of the current primary (health-based) standards. We identified a number of major concerns with the draft that are summarized in the following sections.

PM air pollution is a complex mixture of solid and liquid particles that vary in number, size, shape, surface area, chemical composition, solubility, and origin. Historically, ambient PM air pollution has been regulated in the U.S. by setting national air quality standards for the total mass of particles (irrespective of their chemical composition). Over the years, the focus has changed from consideration of all particles that are suspended in the ambient air to particles within specific size ranges. The draft PA discusses three size ranges of particles: "coarse" particles that have aerodynamic diameters between 10 and 2.5 micrometers (denoted $PM_{10-2.5}$); "fine" particles that have aerodynamic diameters below 2.5 micrometers (denoted $PM_{2.5}$); and "ultrafine" particles that have aerodynamic diameters between 0.01 and 0.1 micrometers. Since the draft concludes that the information is too limited to support a distinct standard for ultrafine PM, a conclusion we agree with, the focus of these comments is on fine and coarse mode particles.

The previous review of PM air quality standards was completed in September 2006 when EPA announced final decisions[3] to revise the primary and secondary NAAQS for PM to provide increased protection of public health and welfare. At that time, EPA revised the level of the 24-h $PM_{2.5}$ standard to 35 $\mu g/m^3$ and retained the level of the annual $PM_{2.5}$ annual standard at 15 $\mu g/m^3$. EPA also retained the 24-h PM_{10} standard of 150 $\mu g/m^3$ and revoked the PM_{10} annual standard because the available evidence did not show a link between long-term exposure to current ambient levels of coarse particles and health effects.

Comments on the discussion of fine PM standards

There are unusually large uncertainties involved in setting PM standards

When the first fine PM standards were set in 1997, the Agency acknowledged that there were unusually large uncertainties involved in setting PM standards relative to setting standards for individual compounds. During the next review, the Agency again acknowledged the unusually large uncertainties in the staff paper that plays a role analogous to the PA in the current review. The uncertainties involve several major factors.

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[2] U. S. Environmental Protection Agency, Policy Assessment for the Review of the Particulate Matter National Ambient Air Quality Standards, First External Review Draft, EPA 452/P-10-003, March 2010.

[3] 71 Federal Register 61144, September 21, 2006.

First, PM is a mixture of many different substances with widely varying toxicities in controlled exposures. Regulating fine PM as if all the components are equally toxic is an assumption that cannot be supported based on the known toxic properties of the individual components. Many years of research on the toxicity of individual PM components demonstrate that the toxicity of PM components per unit of mass varies by a factor of at least 1,000. The toxicological and human clinical evidence for PM mixtures reviewed in the ISA indicates many biological responses but the findings are often mixed and inconsistent and of uncertain clinical relevance. These studies provide limited support for many potential biological mechanisms but have not yet demonstrated how "generic" particles can cause the purported effects at relevant ambient doses.

Second, the evidence used to establish the current PM standards comes almost entirely from epidemiological studies. The March 2009[4] and September 2009[5] AIR comments on the draft ISA provided detailed reasons why the epidemiology summarized in the ISA is highly uncertain. For example, the pattern of acute associations reported for PM is remarkably similar to that of all the criteria pollutants. In addition, multi-city studies report a biologically implausible wide range in individual-city associations from positive to negative for each pollutant. With 25 to 40 percent of the associations in various multi-city studies being negative, it is impossible to characterize the data as consistent. With such stochastic variation, relying on any one individual study or a small cluster of studies is unreliable. Finally, there is now greater appreciation that model selection uncertainty, publication bias, and issues of surrogacy or confounding limit the interpretation of the published associations as true effects.

There is now a comprehensive new study of air pollution associations in 11 Canadian cities using 20 years of data that reinforces the concerns over model selection uncertainty raised in AIR comments

A new study[6] underscores many of the issues raised in the preceding paragraph and adds additional insights as to the reasons why the real relationships between health effects and air pollution at relevant exposures are small and insignificant. In this study, the authors conduct a comprehensive analysis of air pollution morbidity relationships for eleven Canadian cities over a long record from 1974 to 1994. As a result, they have a unique data set that allowed the examination of both spatial and temporal variations. In addition to including the five criteria pollutants, CO, PM, SO_2, NO_2, and O_3, they also controlled for socioeconomic factors, smoking and meteorology. Much shorter subsets of this data

[4] J. M. Heuss and G. T. Wolff, Review and Critique of the U. S. Environmental Protection Agency's First External Review Draft of the "Integrated Science Assessment for Particulate Matter, Air Improvement Resource, Inc. Report, Prepared for The Alliance of Automobile Manufacturers and The Engine Manufacturers Association, March 13, 2009.

[5] G. T. Wolff and J. M. Heuss, Comments on EPA's Second External Draft of the Integrated Science Assessment For Particulate Matter (PM), Air Improvement Resource, Inc. report prepared for the Alliance of Automobile Manufacturers, September 2009.

[6] Koop, G., McKitrick, R. and Tole, L. (2010). Air pollution, economic activity and respiratory illness: Evidence from Canadian cities, 1974-1994. Environ. Model. Softw. Doi.10.1016/j.envsoft.2010.01.010 (in press).

set have been without the socioeconomic and smoking variables by a number of research groups to demonstrate significant relationships with a number of health outcomes and individual pollutants. The long data set enables the present investigators to explore the impact of significantly lower air pollution concentrations at the end of the data set compared to the beginning. Koop et al. also employed the two major methods used to formulate the statistical models in time-series studies: model selection by the use of some statistical criteria and Bayesian Model Averaging (BMA) to address the all-important issue of model selection uncertainty.

As Koop et al. noted for air pollution/mortality or morbidity epidemiology results in general, and we noted in our March, 2009,[7] comments specifically for PM studies, the results are conflicted. In other words, the results range from positive to negative and from significant to insignificant for all pollutants and for all health endpoints. Koop et al. state:

> One of the reasons for this profusion of apparently contradictory results is model uncertainty. With very few exceptions (e.g. Clyde, 2000;[8] Clyde and DeSimone-Sasinowska, 1997[9] and Koop and Tole, 2004,[10] 2006[11]), previous studies on air pollution-health effects have used model selection methods, i.e. choosing one or a few regression specifications and reporting point estimates and their associated variances conditional on that being the true model. However, the estimation exercise is inherently opportunistic. Many plausible covariates could be included, but the choice is not dictated by theory so much as by data availability. Hence there is not only uncertainty about regression slope coefficients conditional on the model selection, but about the model specification itself.[12]

Compounding the issue of selecting the true model is the large number of potential explanatory variables and possible forms that will influence the model results. As Koop et al. articulate it:

> However, the number of potential confounding variables implies that a huge number of models could be used to explain health effects. The number of potential models is on the order of 2^k where k is the number of potential explanatory variables, including lags. Since results can be sensitive to the particular regression specification, and since the number of potential models is so

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[7] Heuss and Wolff, supra note 4.
[8] Clyde, M., 2000. Model uncertainty and health effect studies for particulate matter. Environmetrics 11, 745–764.
[9] Clyde, M., DeSimone-Sasinowska, H., 1997. Accounting for Model Uncertainty in Poisson Regression Models: Particulate Matter and Mortality in Birmingham, Alabama. Institute of Statistics and Decisions Sciences, Duke University Discussion Paper 97-06.
[10] Koop, Gary, Tole, Lise, 2004. Measuring the health effects of air pollution: to what extent can we really say that people are dying from bad air? J. Environ. Econ. Manage. 47, 30–54.
[11] Koop, Gary, Tole, Lise, 2006. An Investigation of thresholds in air pollution mortality effects. Environmental Modelling & Software. 21 (12), 1662–1673.
[12] Koop et. al., supra note 6 at 3.

large, model uncertainty has been shown to be an important issue in this literature (Clyde, 2000; Koop and Tole, 2004).[13]

To address the model uncertainties, the authors use BMA. This method includes information from every potential model. The BMA results are weighted averages of the estimates from each model. The weights are proportional to the support the data give each model.

The results of the BMA analyses show that the health outcomes are explained by the smoking and the socioeconomic variables and that none of the air pollutants showed a statistically positive relationship with health. In fact most pollutant relationships were slightly negative, but not robust. With this particular data set the BMA results were largely similar (except NO_2 showed an effect in a single model) to the results obtained by selecting a single model. This is in contrast to their earlier results (Koop and Tole, 2004[14]) for Toronto which found many relationships when a single model was used. In the earlier paper, a shorter data record was used and the smoking and socioeconomic variables were not included. This may explain the differences and underscores the importance of including these variables in a longer time-series in these types of studies.

In summary, this study demonstrates the importance of: 1) incorporating smoking and socioeconomic variable into the models, 2) using a longer time series that has significantly different pollutant concentrations at the beginning and end of the study, 3) using the BMA approach which minimizes model selection uncertainties and finds insignificant health impacts. This suggests that the epidemiological evidence relied on by EPA in the ISA and PA is scientifically unsound and should not be used as a reason to lower the present suite of PM NAAQS.

The assumption that all fine PM can be treated as equally toxic, that undergirds the preliminary findings, is flawed

The conclusions regarding causality in the 2004 Criteria Document acknowledged some of the concerns regarding the uncertainty with regard to PM epidemiology and refer to "PM (or one or more PM component) acting alone and/or in combination with gaseous pollutants" as likely causing health effects rather than to PM mass alone.

The conclusions regarding causality in the 2009 ISA do not add these qualifications. However, as documented in detail in the March 2009 AIR comments,[15] the pattern of associations in multi-city studies is not consistent with an effect of generic $PM_{2.5}$ mass. There is a spatial and temporal pattern in the associations with little or no association in significant portions of the country and during a significant portion of the year. In addition, a similar spatial pattern is found in acute morbidity and mortality as well as in chronic mortality studies. The ISA and the draft PA acknowledge the heterogeneity and

[13] Ibid at 2.
[14] Koop and Tole supra note10.
[15] Heuss and Wolff supra note 4 at pages 11-13, 26, 34-37, 39-41, 43, 45-49.

spatial patterns in the data at various points, but the ramifications of these differences are not acknowledged. This is a serious flaw.

Based on the patterns in the data, all the considerations of causality in the PA must be qualified as they were in the 2004 Criteria Document to refer to "PM (or one or more PM component) acting alone and/or in combination with gaseous pollutants" rather than to PM mass alone. When the full weight of evidence is considered, the case for causality is weaker than expressed in the document.

The assumption that all fine PM can be treated as equally toxic undergirds a large number of preliminary findings in the draft. Since the assumption is flawed, many of the preliminary conclusions the PA draws are also flawed. In the following, these key findings are discussed.

The evidence from new multi-city studies is not as consistent as portrayed in the PA

In describing the results of new multi-city studies the draft PA indicates that "These studies have reported consistent increases in morbidity and/or mortality related to ambient $PM_{2.5}$ concentrations, with the strongest evidence reported for cardiovascular-related effects."[16] This statement overstates the case for fine PM effects.

As documented in detail in the March 2009 AIR comments, despite the many new studies of cardiovascular endpoints, the estimate of the magnitude of acute cardiovascular effects, such as hospital admissions and ED (emergency department) visits, associated with $PM_{2.5}$ is smaller than thought in 2004-2006. There is also less consistency than thought in 2004. The individual-city results in multi-city acute PM studies demonstrate an implausibly wide range of associations from positive to negative. Based on large multi-city studies, there are spatial and temporal patterns in combined analyses that implicate PM components rather than generic PM mass.

The evidence from new cohort studies is not as consistent as portrayed in the PA

In discussing the long-term studies, the PA indicates "Collectively, these long-term $PM_{2.5}$ exposure studies, along with the evidence available in the last review, provide us with consistent and stronger evidence of associations between long-term exposure to $PM_{2.5}$ and mortality."[17] This statement overstates the case for consistent long-term associations.

The March 2009 AIR comments documented that there are major spatial differences in the full body of cohort studies of chronic mortality. There are several cohort studies in the Western U. S. that report no statistically significant fine PM association. There is also a pattern in acute observational studies with a major difference between associations in the East and West similar to the pattern identified in the chronic mortality studies. Where there are positive chronic fine PM associations, the association is with cardiovascular risk, not respiratory risk. For example, the PA concludes "With respect

[16] PA supra note 2 at page 2-14.
[17] Ibid, at page 2-16.

to respiratory-related mortality associated with long-term $PM_{2.5}$ exposure, evidence is "limited and inconclusive."[18]

The high probability that the association of risk of cardiovascular death in the central and eastern U. S. with $PM_{2.5}$ is unique must be considered in the PA. For example, there is a large cohort study from the Netherlands, Beelen et al., 2008, in which none of the $PM_{2.5}$ associations in the full cohort were statistically significant although the strongest association was with respiratory mortality. Thus, Beelen et al. observed, if anything, a small respiratory signal as compared to the cardiovascular signal in the ACS (American Cancer Society) cohort that EPA relies on in the PA. The inconsistencies in the chronic mortality studies lend additional credence to the conclusion that, to the extent there are positive $PM_{2.5}$ associations, they are caused either by unidentified covariates, by components of PM not PM mass, or by historic high exposures and sources unique to the Eastern U. S.

The PA discussion of the adequacy of the current standards is flawed

The PA indicates, "we reach the preliminary conclusion that there is stronger and more consistent and coherent support for associations between short- and long-term $PM_{2.5}$ exposure and a broader range of health outcomes than was available in the last review, providing the basis for fine particles at least as protective as the current PM standards."[19] As discussed in the above sections, the data is not as strong or consistent as portrayed in the PA. The assumption inherent throughout the document that fine PM can be treated as one species, irrespective of its composition, is scientifically unsound and leads to flawed conclusions.

The PA focuses on the positive associations of fine PM with health endpoints and either downplays or ignores the many negative associations in the multi-city studies that demonstrate a biologically implausible range and the presence of greater stochastic variation than heretofore thought. In addition, the strong spatial and seasonal pattern in combined associations in multi-city studies is also downplayed or ignored. Thus, the PA draws very general and highly qualified conclusions that are scientifically unsound, such as "Multi-city studies support a largely positive and frequently statistically significant relationship between short-term exposure to $PM_{2.5}$ and increased risk of mortality."[20] In reality, if fine PM is causing mortality, it should not be limited to certain regions of the country, or certain seasons, or certain cities. If fine PM is causing mortality, there should not be a strong positive signal in some cities and a strong negative signal in others. The pattern of associations that is observed is not consistent with a health effect that us caused by a real physiological response.

Although there is more data than were available in the previous review, when the full range of associations and the regional and seasonal pattern in the multi-city studies is evaluated, the data are much less consistent and convincing than portrayed in the PA.

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[18] Ibid, at page 2-20.
[19] Ibid, at page 2-25.
[20] Ibid, at page 2-39.

After discussing the observational data in general terms and the results of the draft Risk and Exposure Assessment, the PA indicates:

> We reach the preliminary conclusion that the available information clearly calls into question the adequacy of the current suite of $PM_{2.5}$ standards and provides strong support for giving consideration to revising the current standards to provide increased public health protection.[21]

This conclusion is based on a flawed analysis of the observational data and on a flawed quantitative risk assessment. The draft risk assessment is based on the flawed assumption that all fine PM is equally toxic. In the last review, the Administrator placed little weight on the quantitative risk assessment because it was not clear that controls that would reduce fine PM would also reduce the toxic components. That concern is still relevant. In addition, since there are acute and chronic fine PM associations in cities and regions that are negative or zero, the risk assessment should acknowledge that the lower limit of the risk from attainment of the current standards is zero. For example, Zeger et al., 2008 report a positive association of fine PM with all-cause mortality in the Central and Eastern U. S. where the fine PM concentration averages 10 and 14 $\mu g/m^3$ but a slightly negative association in the Western U. S. where the fine PM averages 13 $\mu g/m^3$. Thus, whether fine PM is harmful or not depends on where you live, not on the fine PM concentrations you are exposed to. In acute studies, fine PM and PM_{10} associations with mortality are positive in some regions and seasons and null in other seasons and/or regions. The draft risk assessment does not display these variations so it is incomplete. Again, the pattern is not consistent with a health effect from fine PM that has a real physiological basis.

Rather than focus on the positive associations and ignore the complete pattern in the data, EPA and the PA should acknowledge the inconsistencies and evaluate all the possible explanations for the patterns in the data. In the draft PA, positive associations are accepted as "real" health effects and null or negative associations are either ignored or dismissed with an explanation that posits a possible reason for the null finding. The strong evidence of stochastic variability as a cause of positive associations is ignored. The strong possibility that PM composition plays a key role in explaining the spatial and temporal patterns is not addressed. The strong possibility that model selection uncertainty and publication bias act together to magnify the apparent magnitude and consistency of the data is ignored. Because of these biases in the evaluation of the data, the preliminary conclusions regarding the adequacy of the current standards are flawed.

The preliminary recommendations for revising the standards, since they are based on biased evaluations of the data, are also flawed

After reaching the preliminary conclusion that calls into question the adequacy of the current suite of $PM_{2.5}$ standards, the draft PA goes on to develop the following

[21] Ibid, at page 2-55.

preliminary recommendations for revising the standards:

> Consideration of a revised annual $PM_{2.5}$ standard within the range of 13 to 12 $\mu g/m^3$, together with either retaining or revising the 24-hour $PM_{2.5}$ standard within the range of 35 to 30 $\mu g/m^3$.
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> Or
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> Consideration of a revised annual $PM_{2.5}$ standard, within the range of 11 to 10 $\mu g/m^3$, together with revising the 24-hour $PM_{2.5}$ standard within a range of 30 to 25 $\mu g/m^3$.

The analysis uses the same biased methods to evaluate the data as is used to evaluate the adequacy of the current standards. The risk assessment assumes causality, equal toxicity, linearity, and positive associations, so it automatically assumes there will be a risk reduction. Since there is uncertainty related to all these assumptions, the risk assessment results should be given little weight.

The analysis of short-term effects in the observational data focuses on the range of 98th percentile values averaged across cities from the multi-city studies. The PA does acknowledge the limitations of single-city studies noting:

> In light of the mixed findings reported in single-city studies, particularly for studies conducted in areas such as Phoenix, Denver, and Edmonton that report both positive and null findings, we place comparatively greater weight on the results from multi-city studies.[22]

However, the way the PA analyzes the multi-city studies aggregates such mixed findings together, obscuring the spatial and temporal patterns, stochastic variation, and range of results in individual cities in the multi-city studies. When the full pattern of results in the multi-city studies is considered, the limitations of using the epidemiological data to set standards are apparent.

The analysis of long-term effects in the observational data focuses on selecting a level somewhat below the long-term mean $PM_{2.5}$ concentrations in the chronic studies that show associations with mortality and cardiovascular and respiratory morbidity. However, there are also long-term studies that show no association at the same or greater fine PM exposures, as shown above.

Tightening the generic fine PM standards without knowing what causes the variations in PM associations from positive to negative, at the same PM exposure, is scientifically unsound, It may or may not affect the public health, and it will divert the nation's resources away from other options.

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[22] Ibid, at page 2-92.

The strong cardiovascular health signal relied upon by EPA is not coherent with fine PM risks in other exposure situations

If low doses of generic ambient fine particles are causing the serious health effects implied by the statistical associations EPA relies on, then low doses of particles should be causing similar effects in other exposure situations. As documented in the ISA, the exposure to nonambient particles is as high or higher than the exposure to ambient particles. Therefore, there should be a health signal for generic particles as measured by mass in the indoor pollution literature. Although there are well-established indoor health risks from environmental tobacco smoke and from particles of biological origin such as house dust-mite, cockroach, and animal allergens, no substantial or consistent health signal from generic PM has been documented. A review of the scientific literature focusing on non-industrial indoor environments looked for evidence of particle health effects.[23] An interdisciplinary group of European researchers surveyed over 10,000 articles by title, chose 1725 abstracts to screen, and chose 70 articles for full review. They concluded that "there is inadequate scientific evidence that airborne, indoor particulate mass or number concentrations can be used as generally applicable risk indicators of health effects in non-industrial buildings." The lack of a health signal from generic indoor PM is not coherent with the assumed presence of a strong outdoor generic ambient PM health signal.

Gamble and Nicolich[24] compared the risks from smoking and occupational exposures with the risks implied by several of the cohort studies that EPA relies on and concluded that the toxicity per unit mass of ambient PM would have to be 2 to 4 orders of magnitude higher than that from smoking to explain the reported ambient risks. The finding led them to conclude that the risks from the cohort studies were not coherent with the risks derived from smoking or occupational studies.

The findings from massive indoor pollutant exposures in developing nations are also relevant. Approximately half the world's population relies on unprocessed biomass fuels (wood, coal, crop residues, or animal dung) for cooking and space heating. These fuels are typically burned indoors in simple unvented cookstoves. The exposures to both gases and particles are many times higher than the indoor exposures in developed countries. For example, a detailed exposure study[25] of 55 households in rural Kenya reports that PM_{10} exposures of adult women (who normally cook and tend the fire) were

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[23] Schneider, T.; Sundell, J.; Bischof, W.; Bohgard, M.; Cherrie, J. W.; Clausen, P. A.; Dreborg, S.; Kildeso, J.; Kjaergaard, S. K.; Lovik, M.; Pasanen, P.; Skyberg, K.; EUROPART. Airborne Particles in the Indoor Environment. A European Interdisciplinary Review of Scientific Evidence on Associations between Exposure to Particles in Buildings and Health Effects, *Indoor Air*, **2003**, *13,* 38-48..

[24]. Gamble J. F.; Nicolich, M. J.; Comparison of Ambient PM Risk with Risks Estimated from PM Components of Smoking and Occupational Exposures, *J. Air & Waste Manage. Assoc*., **2000**, *50*, 1514-1531.

[25] Ezzati, M.; Saleh, H.; Kammen, D. M.; The Contributions of Emissions and Spatial Microenvironments to Exposure to Indoor Air Pollution from Biomass Combustion in Kenya, Environmental Health Perspectives, 2000, 108, 833-839.

the order of 5 mg/m^3 while adult male exposures were the order of 1 mg/m^3. These levels are 40 to 200 times higher than the current average U. S. outdoor PM_{10} levels of 25 μg/m^3. A 2002 World Health Organization report[26] of the health effects of indoor pollution exposures in developing countries reviews the evidence for health effects from these exposures. While there is strong evidence of important effects on acute and chronic respiratory disease in many countries and effects on lung cancer from coal use in China, there is little evidence to date of a strong cardiovascular signal from these massive exposures.

Yusuf et al., 2001[27] discuss the global burden of cardiovascular disease in detail. A comparison of the overall cardiovascular heart disease rates in various areas of the world together with urban/rural and male/female differences in countries like China and India that have large populations and massive biomass fuel exposures reveals little support for fine PM being a significant cardiovascular risk factor. This also does not appear to be coherent with the assumption of a strong cardiovascular signal from low doses of generic ambient fine PM.

EPA should not tighten the current fine PM standards based on questionable assumptions without addressing the coherence of the PM risks they posit with the risks observed or not observed in other PM exposure situations.

Comments on the discussion of thoracic coarse PM standards

In the Policy Assessment document,[28] EPA concludes that "either a PM_{10} or a $PM_{10-2.5}$ indicator would be expected to provide protection against all ambient mixes of thoracic coarse particles, as long as these indicators were not qualified so as to exclude certain types of sources or locations." They further note "recent studies do provide some evidence for the toxicity of particles from a variety of environments, including particles of non-urban origin."[29] Thus, EPA has decided that urban and rural thoracic PM should be treated equally. From an implementation perspective, we think this is a sound decision because the tools to distinguish the origins of individual thoracic PM do not exist.

Concerning the level of the standard, EPA is less decisive: "we will consider a range of potential alternative standards levels for a PM_{10} standard."[30] The reason they will

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[26] Bruce, N.; Perez-Padilla, R.; Albalak, R.; The health effects of indoor air pollution exposure in developing countries, World Health Organization Report WHO/SDE/OEH/02.05, 2002.

[27] S. Yusuf, S. Reddy, S. Ôunpuu and S. Anand, Global Burden of Cardiovascular Diseases: Part I: General Considerations, the Epidemiologic Transition, Risk Factors, and Impact of Urbanization, Circulation, 2001;104;2746-2753 DOI: 10.1161/hc4601.099487; S. Yusuf, S. Reddy, S. Ôunpuu and S. Anand, Global Burden of Cardiovascular Diseases: Part II: Variations in Cardiovascular Disease by Specific Ethnic Groups and Geographic Regions and Prevention Strategies, Circulation, 2001;104;2855-2864 DOI: 10.1161/hc4701.099488.

[28] PA supra note 2 at page 3-33.

[29] Ibid.

[30] Ibid, page 3-38.

consider a range is because: "our preliminary conclusion is that the available evidence could support either revising the current PM_{10} standard to increase public health protection against exposures to thoracic coarse particles or retaining the current PM_{10} standard, depending on the emphasis placed on different aspects of the evidence and associated uncertainties."[31] The public health concerns that are motivating this are the conclusions from the PM ISA which states that the evidence is "suggestive" of a causal relationship between short-term $PM_{10-2.5}$ exposures and mortality, cardiovascular effects and respiratory effects.[32] Consequently EPA's decision on the level of the standard depends upon the emphasis they place on the "associated uncertainties" of the epidemiological studies which provided evidence that EPA has interpreted as "suggestive" of causal relationships.

While it is encouraging that EPA recognizes that the epidemiology studies suffer from uncertainties, their preliminary discussion of the uncertainties in the Policy Assessment document[33] fails to include a discussion of the most important uncertainty, model selection. An important recent study by the Health Effects Institute addresses some aspects of the model selection issue specifically for PM_{10}.

The combined results of the large and comprehensive APHENA study are not consistent with PM_{10} having a causal role in mortality or morbidity below the current standard.

In October, 2009, the Health Effects Institute (HEI) published the results of the *Air Pollution and Health: A European and North American Approach (APHENA)*[34] study. The APHENA project was designed to take advantage of the largest databases available. These had been developed by the three groups of investigators for earlier studies: 1) the *Air Pollution and Health: A European Approach* Phase 2 (APHEA2) study involving 32 cities; 2) the National Morbidity, Mortality, and Air Pollution Study (NMMAPS), conducted in the 90 largest U. S. cities; and 3) multicity research on the health effects of air pollution in 12 Canadian cities. Each database included air pollution monitoring data for particulate matter and ozone, health outcome data in the form of daily mortality for all ages, for persons younger than 75 years, and for persons 75 years or older (from all nonaccidental causes [all cause]), cardiovascular disease, or respiratory disease) and daily hospital admissions for persons 65 years or older (for cardiovascular and respiratory disease). Other database variables used for APHENA included weather data and a number of socioeconomic and other variables known or suspected to influence mortality or hospital admissions.

In the original studies, each of the three groups used different modeling methodologies and entered different variables into their models. Although each group found positive and significant relationships between PM_{10}/O_3 and mortality and some morbidity

[31] Ibid, page 3-25.
[32] U.S. EPA, supra note 1 at 2-19.
[33] PA supra note 2 at 3-20 to 3-22.
[34] Katsouyanni K. and Samet, J. (2009). Air Pollution and Health: A European and North American Approach (APHENA), HEI Report 142, October, 2009.

endpoints, the magnitude of the relationships differed by geographic region. One goal of APHENA was to use common methodologies and variables and reanalyze their data sets. They intended to create a central repository for all three of the time-series databases and use a common quality assurance approach. In addition, they would conduct analyses on a combined, pooled dataset to study a variety of sensitivity issues including effect modification. They would then investigate the sensitivity of the estimates to a variety of smoothing methods and to the number of degrees of freedom. They also intended to explore reasons for the geographical heterogeneity of the effect estimates seen in their original studies. Another important goal of the program was to understand the extent of coherence between mortality and hospitalizations using data from cities in North America and Europe.

In the original analyses, all three groups used a two-stage approach. In the first stage, risks were estimated for the individual cities, and in the second stage, evidence across the cities was combined. Each group used different methods to perform both stages in the original analyses. In APHENA, the investigators wanted to identify a preferred way to do both stages and apply common methodologies to the three data sets. For the first stage, they identified two smoothing techniques, natural splines (NS) and penalized splines (PS), and decided to use a number of degrees of freedom choices. They chose to use 3, 8 and 12 degrees of freedom and also the number of degrees of freedom chosen by minimizing the partial autocorrelation function (PACF).

For the second stage analyses, the two approaches used in original NMMAPs and the European studies represented the two major approaches used at the time to pool estimates. NMMAPS used Bayesian hierarchical regressions models while the Europeans used metaregression models. However, they could not determine which method was best, so they decided to use the models interchangeably. Using the two smoothing techniques together with the four choices for the degrees of freedom and three choices of lags (0-1 day, 1 day and distributive lags which provided the cumulative effects of days 0 through 2) for each health outcome, the investigators ran a total of 24 different models for PM_{10}. In addition, subsets of these choices were also used to examine the effects of controlling for ozone. The results showed that the differences between the PS and the NS were very small in most cases and that the number of degrees of freedom tended to give similar results when greater than 6-8 degrees of freedom where used.

The overall modeling results for the mortality models and the morbidity models are summarized in Tables 1 and 2, respectively. The denominator in the tables is the total number of different models that were run for each health effect outcome examined and the numerator is the number of models that resulted in a positive and statistically significant relationship between PM_{10} and the health effect outcome. The way to interpret these tables is as follows. High ratios are suggestive of a robust and consistent relationship while low ratios are suggestive of no significant relationship. Intermediate values of the ratio suggest inconsistent and non-robust relationships that are dependent upon the model selected. Since there is no a priori way to determine the “correct” model, it is not possible to determine whether a significant and positive relationship represents

real causal relationship or if they are false positives that can occur by chance or by confounding.

For mortality, the strongest and most consistent significant relationships are observed for all cause and cardiovascular mortality, but only for the ≥ 75 years age group in Canada and Europe. Importantly, the signal is inconsistent in the U. S. as it is model dependent. For the younger age group, few models are significant except in Europe for all cause but not cardiovascular or respiratory. None of the three geographic areas show consistent significant positive model results for respiratory mortality. Further, none of the models in Canada produce significant results for respiratory mortality.

The models also show mixed results for the hospital admissions. The most consistent significant positive signal is seen for cardiovascular admissions in the U. S. and to a slightly less degree in Europe. However, none of the model formulations produce significant results in Canada. No consistent results are seen for respiratory admissions anywhere. They are strongly model dependent.

The above results from the APHENA study demonstrate the importance of model selection. However, APHENA did not undertake an exhaustive, comprehensive analysis of model selection as they include a limited number of model choices and only considered two pollutants, PM_{10} and ozone. Another recent study that underscores the importance of model selection is the Koop et al. (2010) study[35] discussed earlier.

While there are positive and significant combined associations for some models and for some endpoints and for some geographic areas, the overall pattern of associations in the large APHENA study is mixed and inconsistent. The overall pattern is not what one would expect if PM health effect associations have a real physiological basis. For example, it is not logical that PM would be causing cardiovascular hospital admissions in the U. S. but not in Canada. It is not logical that PM would have a strong cardiovascular mortality signal in Canada but not in the U. S.

The APHENA study is relevant to the consideration of both fine and coarse PM health effects, since PM_{10} is the sum of fine and coarse PM. With respect to both fine and coarse PM standards, the overall inconsistencies and the importance of model selection uncertainty argue against using selected individual city results to tighten the $PM_{2.5}$ and PM_{10} standards.

[35] Koop et al., supra note 6.

Table 1: APHENA modeling results for mortality. The numerators represent the number of models that showed a positive and statistically significant relationship between PM_{10} and mortality while the denominator is the total number of models run.

Cause of Death	Canada	Europe	United States
All Cause – all ages	8/8	18/24	15/24
≥ 75 yrs	8/8	21/24	15/24
< 75 yrs	4/8	16/24	8/24
All Cause ozone controlled – all ages	8/8	16/16	9/16
≥ 75 yrs	8/8	13/16	10/16
< 75 yrs	0/8	13/16	4/16
Cardiovascular – ≥ 75 yrs	8/8	19/24	16/24
< 75 yrs	0/8	8/24	2/24
Cardiovascular –ozone controlled ≥ 75yrs	7/8	16/16	10/16
< 75 yrs	0/8	6/16	2/16
Respiratory – all ages	0/8	11/24	7/24
≥ 75 yrs	0/8	11/24	4/24
Respiratory – ozone controlled – all ages	0/8	7/16	3/16
≥ 75 yrs	0/8	7/16	3/16

*Denotes the PM controlled ratio

Table 2: APHENA modeling results for hospital admission for patients 65 years and older. The numerators represent the number of models that showed a positive and statistically significant relationship between PM_{10} and admissions while the denominator is the total number of models run.

Type of Admission	Canada	Europe	United States
Respiratory	2/8	16/24	9/24
Respiratory – ozone controlled	0/8	10/16	10/16
Cardiovascular	0/8	20/24	24/24
Cardiovascular – ozone controlled	0/8	12/16	16/16