

Comments on EPA's Draft Integrated Review Plan for Particulate Matter

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Executive Summary

Air Improvement Resource, Inc. reviewed the Draft Plan and concludes:

- When the first PM_{2.5} standards were set in 1996/7, EPA acknowledged unusually large uncertainties associated with establishing standards for PM compared to individual gaseous pollutants. Now 20 years later, the unusually large uncertainties still persist.
- There are major patterns in the observational data that are not consistent with the assumptions of causality, equal toxicity, and no threshold that undergird the Agency's NAAQS decisions and control actions.
 - In addition to the limitations of epidemiology acknowledged by EPA, there is strong evidence of stochastic (random) variability that has not been acknowledged by EPA
 - There is evidence of geographic heterogeneity in the chronic studies that demonstrate major differences between the Eastern and Western US and Europe. These differences should be evaluated carefully in the next review
- The ISA should evaluate the coherence between the toxicological data on PM components and the assumption that all PM_{2.5} can be treated as equally toxic
 - Important information on PM health risks in other settings should be considered by the Agency. For example, 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.
 - The risks in various high exposure situations are also relevant to identifying which components or mixtures are important to control. The ISA should rigorously evaluate the occupational literature to identify PM sources or mixtures that are particularly toxic or non-toxic.
 - We urge the Agency to use the literature from controlled studies and different exposure settings to rigorously evaluate dose plausibility for the

various PM components.

- Finally, EPA has built a narrative around the assumed PM mortality effects that dominates the Agency's actions. It is based on the assumptions that PM is causing premature mortality at current ambient concentrations, that there is no threshold and that all PM is equally toxic. The review should rigorously evaluate the evidence for and against these key assumptions.

Introduction

As EPA initiates the next review of the ambient particulate matter air quality standards, the Agency prepared the Draft Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter¹ for Clean Air Scientific Advisory Committee (CASAC) and public review. Air Improvement Resource, Inc. reviewed the draft for the Alliance of Automobile Manufacturers and offers the following comments, focusing on the review of the primary (health-based) standards.

The unusually large uncertainties involved with setting particulate matter (PM) standards still persist

When the first PM_{2.5} standards were set in 1996/7, the EPA acknowledged that there were unusually large uncertainties associated with establishing standards for PM compared to individual gaseous pollutants. The Agency went on to list nine major areas of uncertainty.² In 2005, EPA reiterated the fact that setting air quality standards for particulate matter involves unusually large uncertainties relative to setting standards for other single component pollutants.³ The acknowledged uncertainties led the EPA and the scientific community to ask for and receive greatly expanded federal funding for PM air pollution research. Since 1997, there has been greatly expanded research on PM health effects guided by input from a blue-ribbon National Research Council Panel. Although that research has resulted in a large number of new studies over what is now approaching two decades, there is still a great deal of uncertainty as to how to interpret all of the various results. Samet,⁴ in a 2005 paper, summarized his perspective on the activities of the National Research Committee on Research Priorities for Airborne Particulate Matter, notes that using large databases, relatively weak signals of the health

¹ U. S Environmental Protection Agency, Office of Air Quality Planning and Standards, Draft Integrated Review Plan for the National Ambient Air Quality Standards for Particulate Matter, April 2016.

² U. S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information- OAQPS Staff Paper, EPA-452\R-96-013, July 1996 at pages VII-41 to VII-44.

³ U. S. Environmental Protection Agency, Review of the National Ambient Air Quality Standards for Particulate Matter: Policy Assessment of Scientific and Technical Information- OAQPS Staff Paper, EPA-452\R-05-005, June 2005 at page 5-71.

⁴ J. Samet, "The Perspective of the National Research Council's Committee on Research Priorities for Airborne Particulate Matter," *J. of Toxicology and Environmental Health*, Part A, 68, 1063-1067 (2005).

effects of air pollution have been detected. He went on to indicate that although these small increases in relative risk signal an adverse health effect, there is uncertainty as to the long-term implications of the findings and the overall health impact. He particularly noted the slow progress in identifying the hazardous components of particulate matter. He also noted that with increasingly sophisticated and sensitive indicators of biological response, including various biomarkers, effects of air pollution exposure on biological systems that are of uncertain health relevance can be detected.

The uncertainties primarily arise because the Agency is trying to regulate the complex mixture of many different chemical and physical aerosol components based only on their mass as particles using primarily observational data that is not conducive to evaluating causality. As Green et al. pointed out in 2002,⁵ it makes no more sense to estimate the health effects of all particles in the air by their mass as it would to consider the health effects of all the gases in the air based on their contributions to mass.

The assumption of equal toxicity by mass was the focus of HEI's NPACT study, which was initiated in 2005 and completed in 2013. Our reading of the NPACT reports is that they are not particularly helpful in resolving the controversy over the assumption of equal toxicity. There is not much consistency or coherence in the results. There are inconsistent and unexpected results in the studies as well as differences of opinion between the investigators and the HEI Review Committee as to the interpretation and significance of the results.

In addition, Harrison⁶ in a recent paper entitled "Air pollution and human health: Where does the latest evidence lead us?" indicates:

There has been intensive research aimed at elucidation of which of the characteristics of airborne particles (e. g. chemical composition, size association or source) is primarily responsible for the adverse health consequences of exposure, and the results of the recent NPACT study in the US and the RAPTES study in the Netherlands are reviewed and the conclusion drawn that no clear inference can currently be drawn as the ranking of toxicity of specific components, or even of size fractions.

The Draft Plan acknowledges a number of the major uncertainties.

There are major patterns in the observational data that are not consistent with the assumptions of causality, equal toxicity, and no threshold

- **In addition to the limitations of epidemiology acknowledged by EPA, there is strong evidence of stochastic (random) variability that has not been acknowledged by EPA**

⁵ Green, LC et al. What's Wrong with the National Ambient Air Quality Standard (NAAQS) for Fine Particulate Matter (PM_{2.5})? *Regulatory Toxicology and Pharmacology*, **35**, 327-337, 2002.

⁶ Harrison, RM, Air pollution and human health: Where does the latest evidence lead us? *Air Quality and Climate Change*, **47**, 26-31, 2013.

It has been known for a long time that there are severe limitations to the use of epidemiology to try and tease out interactions and to evaluate causality. A meta-analysis by Steib et al. (2002, 2003)⁷ evaluated 109 acute mortality studies from around the world. They reported that there are positive associations with mortality (with a wide range in the individual cities) for all the major pollutants in single pollutant models and that for each, when other pollutants are included, the association with the first pollutant, on average, is decreased. In fact, the patterns in single-pollutant epidemiological studies were remarkably similar for all the criteria pollutants.

The studies evaluated by Steib et al. are all subject to publication bias. Goodman⁸ cautions that “depending on published single-estimate, single-site analyses are an invitation to bias.” He notes that “the most plausible explanation ... is that investigators tend to report, if not believe, the analysis that produces the strongest signal; and in each single-site analysis, there are innumerable model choices that affect the estimated strength of that signal.” To avoid publication bias that would inflate the apparent association, investigators have carried out large multi-city analyses. In fact, the patterns in single-pollutant associations in multi-city epidemiological studies are also very similar for all the criteria pollutants. The individual-city associations in large multi-city studies, such as NMMAPS, cover a biologically implausible wide range from strongly negative to strongly positive at each lag evaluated, a finding which is readily apparent but seldom discussed.⁹

Air pollution time-series epidemiology studies suffer from problems associated with publication bias, model uncertainty, model selection issues, lack of adequate control for confounding variables such as other pollutants and weather, and exposure misclassification arising out of the poor correlation between ambient monitors and personal exposure. In a June 2006 letter to the Administrator, CASAC confirmed this view in evaluating mortality time-series studies, noting that “[b]ecause results of time-series studies implicate all of the criteria pollutants, findings of mortality time-series studies do not seem to allow us to confidently attribute observed effects specifically to individual pollutants.”¹⁰

⁷ Steib, DM; Judek, S; Burnett, RT. (2002) “Meta-analysis of time series studies of air pollution and mortality: Effects of gases and particles and the influence of cause of death, age, and season,” *J. Air & Waste Manage. Assoc.*, **52**: 470-484 and Steib, DM et al. (2003) *J. Air & Waste Management Association*, **53**: 258- 261.

⁸ S. Goodman, “The Methodologic Ozone Effect,” *Epidemiology*, 16, 430-435 (2005).

⁹ When the individual city data for the NMMAPS re-analysis were posted on the Johns Hopkins website, the data showed a remarkable similarity in that there was a biologically impossible wide range of associations from positive to negative for each pollutant for each lag that was evaluated. This data was provided to EPA and CASAC during the PM review process; J. Heuss, Comments on the 4th Draft Criteria Document for Particulate Matter, AIR, Inc. comments prepared for the Alliance of Automobile Manufacturers, August 20, 2003.

¹⁰ Henderson, R. (2006) CASAC Letter, EPA-CASAC-06-07, June 5, 2006 at page 3.

There is also strong evidence for unrecognized stochastic (or random) variability in associations within a given city. In 2003, Ito¹¹ re-analyzed the 1220 separate air pollution mortality and morbidity associations that were included in the original Lippmann et al. 2000 HEI study of Detroit. As shown in Figure 1 (Ito's Figure 2), there was a wide range of negative and positive risks in Detroit when all pollutants, lags, and endpoints were considered. Ito shows in separate figures that the wide range of associations occurred for each pollutant. Although the focus in the original Lippmann study, as it is in almost all the published literature, was on positive associations, Ito's plots shows that there are many negative associations in the data. Although there may be somewhat more positive associations than negative associations, there is so much noise or variability in the data, that identifying which positive associations may be health effects and which are not is beyond the capability of current methods.

% excess risk per 5th-to-95th %ile air pollutants for all outcomes, lags, and air pollutants

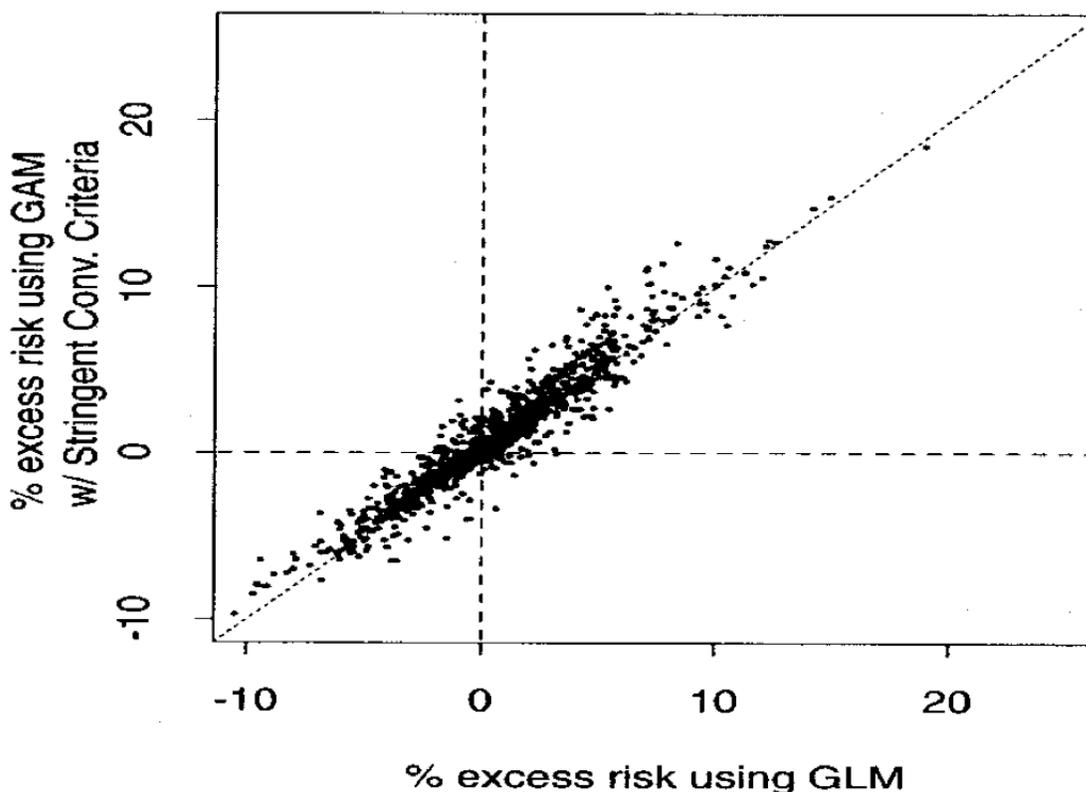


Figure 1: Percent Excess Risk for all pollutants, lags, and outcomes in Generalized Additive Models versus Generalized linear Models.

¹¹ Ito K. 2003. Associations of particulate matter components with daily mortality and morbidity in Detroit, Michigan. In: Revised Analyses of Time-Series Studies of Air Pollution and Health; Revised Analyses of the National Morbidity, Mortality, and Air Pollution Study, Part II. Special Report. Boston, MA: Health Effects Institute.

Additional evidence for substantial stochastic variation comes from an HEI study¹² that evaluated coherence between the time-series associations of mortality and hospital admissions in 14 cities. That study found little or no coherence between the PM₁₀ mortality and morbidity associations and, importantly, found little or no correlation between the time series of health event counts (mortality and hospital admissions) in the various cities. As in other multi-city studies, the individual associations for mortality and morbidity covered a wide range from positive to negative. Finally, there is also a great deal of stochastic variation in the ESCAPE meta-analyses of European mortality cohort studies.

- **There is evidence of geographic heterogeneity that should be evaluated carefully in the next review**

The previous PM review acknowledged that there is heterogeneity in the observed PM associations. There are spatial differences and inconsistencies in the chronic mortality studies; for example, the HEI-sponsored re-analysis of the Six-City and ACS studies (Krewski et al., 2000)¹³ showed that the increased risk was cardiovascular not respiratory, and there was significant spatial heterogeneity in the association, with no effect seen in western U. S. cities. In fact, a negative estimate of excess PM_{2.5} mortality risk was found in the West. Krewski et al. also identified other patterns in the data including: SO₂ had a strong association with mortality, the PM all-cause mortality association was significantly reduced and became non-significant when SO₂ was added in a two pollutant model, and the increased mortality only occurred in the participants that had a high school education or less.

The analysis by Zeger et al. (2008)¹⁴ confirms the large spatial difference in chronic mortality association in a cohort of 13 million Medicare enrollees. Zeger et al. reported statistically significant results for the eastern and central United States that are in general agreement with previous publications, but Zeger et al. found no significant effect of PM_{2.5} on mortality in the western United States. There are also cohort studies in California that support a lack of association in the West with PM_{2.5}, the Chen 2005 study and another by Enstrom.¹⁵ In addition, a recent paper by Young and Xia¹⁶ re-analyzed the data used by Pope et al. in their 2009 NEJM paper and showed that there was no association of PM_{2.5} with longevity in the West.

¹² Dominici, F et al. (2005) HEI Research Report 94, Part IV Health Effects Institute.

¹³ D. Krewski, R.T. Burnett, M.S. Goldberg, K. Hoover, J. Siemiatycki, M. Jerrett, M. Amramowicz, and W. H. White, *Reanalysis of the Harvard Six Cities Study and the American Cancer Study of Particulate Air Pollution and Mortality*, Health Effects Institute Special Report, Cambridge, MA, 2000.

¹⁴ S. Zeger, F. Dominici, A. McDermott and J. Samet, "Mortality in the Medicare population and chronic exposure to fine particulate air pollution in urban centers (2000-2005)", *Environ. Health Perspect.*, 116:1614-1619, 2008.

¹⁵ J. E. Enstrom, Fine particulate air pollution and total mortality among elderly Californians, 1973–2002, *Inhalation Toxicology*, 17: 803–816, 2005.

¹⁶ S. Young and J. Xia, "Assessing Geographic Heterogeneity and Variable Importance in an Air Pollution Data Set," *Statistical Analysis and Data Mining*, 6:375-386, 2013.

The largest hospital admissions study also clearly shows differences in associations with cardiovascular hospital admissions between East and West. The Dominici et al. (2006)¹⁷ study evaluated fine PM hospital admissions associations for 204 U. S. urban counties with a population greater than 200,000 using 1999-2002 Medicare hospital admission data. The authors present results from seven separate regions as well as a comparison of the three western regions with the four eastern regions. There is a clear difference in the combined associations among the regions and particularly between the eastern and western regions. The combined association is positive for cardiovascular outcomes in the east, but negative in the west except for heart failure that is positive in both areas. This is not consistent with an effect of generic PM_{2.5} on cardiovascular hospital admissions and, indeed, the authors point out the need to shift the focus of research to identifying those characteristics of particles that determine their toxicity

Interestingly, there was a major difference in plaque progression in the Western versus Eastern sites in the NPACT sub-chronic CAPs exposure study of Apoe mice, with no plaque progression in the two Western sites, Irvine and Seattle, compared to the filtered air controls.

The Health Effects Institute's Health Research Committee Commentary on the Krewski et al., 2009 study concludes "with the emergence of new cohort evidence from the United States and Europe — the similarities and differences among the results of the various studies need to be examined closely."¹⁸

With the advent of several new papers on the European experience, a close examination of the similarities and differences between the reported associations in the Eastern U. S., Western U. S. and Europe is now possible. In various European meta-analyses, Dimakopoulou, et al.¹⁹ report no association of PM_{2.5} with non-malignant respiratory mortality in 16 cohorts, and Beelen, et al.²⁰ report the association of air pollutants with mortality from overall cardiovascular and from specific CVDs were approximately 1.0 in 22 European cohort studies, with the exception of particulate mass and cerebrovascular disease mortality for which there was suggestive evidence for an association. If PM_{2.5} is causing premature mortality, these two major categories of disease are where the effect is expected or most likely to occur.

¹⁷ F.D. Dominici, D. Peng, M. Bell, A. Pham, A. McDermott, S.L. Zeger and J.M. Samet, "Particles, air pollution and hospital admissions for cardiovascular and respiratory diseases." *J. American Medical Association*, 295:1127-1134, 2006.

¹⁸ Health Effects Institute Research Report 140, Health Effects Institute, Boston, Massachusetts, at page 134.

¹⁹ K. Dimakopoulou, E. Samoli, et al. Air Pollution and Nonmalignant Respiratory Mortality in 16 Cohorts within the ESCAPE Project, *American Journal of Respiratory and Critical Care Medicine*, 189: 684-696, 2014.

²⁰ R. Beelen, et al. Long Term Exposure to Air Pollution and Cardiovascular Mortality: An Analysis of 22 European Cohorts, *Epidemiology*, 25: 368- 378, 2014

In contrast, Beelen et al.²¹ report that there is a small positive association of PM_{2.5} with all natural-cause mortality in the European cohorts. Beelen et al. acknowledge that they do not have a clear explanation for the lack of an association with cardiovascular mortality within the ESCAPE project, when they found an association with all natural-cause mortality. Clearly, there are major differences between the pattern of associations in Europe, the Western U. S., and the Eastern U. S. Therefore, the next ISA should be focused on evaluating spatial heterogeneity and what it means with regard to the support for causality, equal toxicity, and dose-response assumptions.

The ISA should evaluate the coherence between the toxicological data on PM components and the assumption that all PM_{2.5} can be treated as equally toxic

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. Treating all PM_{2.5} as if it were equally toxic is a gross simplification that is not consistent with the large body of toxicological data on either individual PM_{2.5} components or ambient PM_{2.5} mixtures. The 2004 CD indicated that different PM materials also vary extensively in toxicity, based on over 30 years of toxicological study.²² This substantial body of information is routinely used to establish chemical-specific standards that are used in occupational and other settings, and demonstrates that the relative toxicity of different PM species per unit mass varies by over three orders of magnitude.²³

We now have considerable information on the composition of ambient PM and human exposures to PM of ambient origin. This information should be used together with the body of toxicological data on individual components to evaluate the kinds of effects and levels that may cause those effects expected from exposures to the components of ambient PM. Valberg²⁴ addressed this issue and reported a major disconnect between the application of chemical-specific health effects data using standard EPA health risk assessment procedures and the application of epidemiological associations in the PM review. Valberg reported that the chemical constituents of ambient PM are present at concentrations considerably below the regulatory thresholds used in risk assessment (that is, the levels for which no adverse health effects are anticipated). He concluded that the health effects attributed to ambient PM in the NAAQS review “appears to be at odds with what would be predicted from a standard U.S. EPA health-risk assessment for PM chemicals.” The findings from his analysis should be integrated into the discussion of the toxicology of PM mixtures in the ISA.

²¹ Beelen R, Raaschou-Nielsen O, Stafoggia M, Andersen ZJ, Weinmayr G, Hoffmann B, et al. Effects of long-term exposure to air pollution on natural-cause mortality: An analysis of 22 European cohorts within the multicentre escape project. *The Lancet* 383:785-795, 2014.

²² U. S. Environmental Protection Agency, Air Quality Criteria for Particulate Matter, Volume I, EPA/600/P-99/002aF, October 2004; Volume II, EPA/600/P-99/002bF, October 2004, at page 7-85.

²³ Threshold Limit Values for Chemical Substances in the Work Environment, published Annually by the American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio.

²⁴ P. Valberg, *Inhalation Toxicology*, **16**, Issue 11, Supplement 1, pages 19-29 (2004).

Important information on PM health risks in other settings should be considered by the Agency

There are several bodies of scientific information concerning health risk that are relevant to the ISA's judgments regarding the risk from ambient PM that have not historically been considered in the PM review. These include the observed risks from PM exposures due to PM other than ambient particles, the risks and effects identified in toxicological studies of PM components as noted above, the risks and effects from exposure to other components of the ambient air pollution mix, and the risks associated with changes in weather and weather variables. The rationale for why each of these categories of information is relevant to the ISA is provided below.

- **If low doses of generic ambient particles were causing the serious health effects implied by the acute and chronic PM associations relied on by the Agency, then low doses of particles should be causing similar effects in other exposure settings.**

As noted in the 2004 CD and in the 2009 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.²⁵ 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.

- **The risks in various high exposure situations are also relevant to identifying which components or mixtures are important to control**

Gamble and Nicolich²⁶ compared the risks from smoking and occupational exposures with the risks implied by several of the cohort studies and concluded that the toxicity per unit mass of ambient PM would have to be 2 to 4 orders of magnitude higher than that

²⁵ 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.

²⁶ 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.

from smoking to explain the reported ambient risks. That 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 ISA should rigorously evaluate the occupational literature to identify PM sources or mixtures that are particularly toxic or non-toxic.

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. Those 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 study²⁷ of 55 households in rural Kenya reports that PM₁₀ exposures of adult women (who normally cook and tend the fire) were on the order of 5 mg/m³ while adult male exposures were on the order of 1 mg/m³. These levels are 40 to 200 times higher than the current average U. S. outdoor PM₁₀ levels of 25 µg/m³. A 2002 World Health Organization report²⁸ 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 was little evidence to date of a strong cardiovascular signal from these massive exposures. For example, the review by Fullerton et al.²⁹ notes the paucity of data on cardiovascular effects of biomass burning. Thus the evidence from biomass burning does not appear to be coherent with the assumption of a strong cardiovascular signal from low doses of generic ambient PM.

As part of the integrative discussion of coherence in the ISA, the risks (or lack thereof) in these other exposure settings should be evaluated and compared to the reported risks from ambient observational studies.

- **The extent to which weather systems, weather variables, and/or changes in weather can cause the health effects or biological changes similar to those attributed to PM should be fully evaluated.**

In reviewing the outcome of the 2004 CD, the first draft ISA in 2008 noted that epidemiologic studies have used a variety of approaches to control for weather effects to try to disentangle the true effect due to PM.³⁰ The text referred to studies “that appear to demonstrate increased PM-related mortality/morbidity risks beyond those attributed to

²⁷ 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.

²⁸ N. Bruce, R. Perez-Padilla, and R. Albalak, The health effects of indoor air pollution exposure in developing countries, World Health Organization Report WHO/SDE/OEH/02.05, 2002.

²⁹ Fullerton D. G.; Bruce N.; Gordon S. B. Indoor air pollution from biomass fuel smoke is a major health concern in the developing world, *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **2008**, *102*, 843—851

³⁰ U. S. Environmental Protection Agency, First external review draft of the Integrated Science Assessment for Particulate Matter, EPA/600/R-08/139, December 2008, at pages 6-2 and 6-3.

weather influences alone.” However, the text also acknowledged that a clear consensus was not reached as to what constitutes an appropriate or adequate model to control for possible weather contributions to the mortality/morbidity effects attributed to PM exposure. Thus, the extent to which inadequate control for weather may be biasing or confounding the PM and other air pollution health associations is not known. There is an extensive body of bio-meteorological information which should be evaluated to determine (1) how the nature and magnitude of weather effects compares to the nature and magnitude of air pollution effects, (2) whether current approaches to control for weather are consistent with the current understanding in biometeorology regarding the variables and timeframes involved, and (3) whether the understanding of the mechanisms of weather effects can inform the PM/health effects issue.

After 50 years of air pollution research and 20 years of focused research on PM_{2.5}, it is time to re-think how NAAQS reviews are conducted

For the current review, there is a massive amount of new literature to evaluate and put into perspective with the prior literature. As EPA has reviewed the various pollutants, each ISA has focused on single-pollutant models in the observational studies with limited discussion of potential confounders and claimed independent effects for the pollutant under consideration. With the gaseous pollutants, there is an accompanying body of controlled studies that can be used to evaluate the plausibility of the effects implied by the epidemiological associations both in terms of the types of effects and the doses that may cause effects. In the case of PM, EPA has relied on the observational (epidemiological) database with limited use of the toxicological literature. In the upcoming review, we urge the Agency to use the literature from controlled studies and different exposure settings to rigorously evaluate dose plausibility for the various PM components.

In addition, we urge the Agency to focus on the major uncertainties that have been identified by the Administrator or by CASAC and public comments. For example, the Draft Plan indicates that at the end of the prior review:³¹

The Administrator recognized that uncertainties remained in the scientific information. She specifically noted uncertainties related to understanding the relative toxicity of the different components in the fine particle mixture, the role of PM_{2.5} in the complex ambient mixture, exposure measurement errors in epidemiologic studies, and the nature and magnitude of estimated risks related to relatively low ambient PM_{2.5} concentrations. Furthermore, the Administrator noted that epidemiologic studies had reported heterogeneity in responses both within and between cities and in geographic regions across the U.S.

Additional major uncertainties in the observational database arise due to publication bias, model selection uncertainty, and stochastic variability. There is also an issue of selective presentation of results that can affect both individual studies and EPA’s choices for how to summarize and present the various studies in the literature.

³¹ Draft Plan, *supra* note 1, at page 2-9.

Finally, there is also a new source of uncertainty identified in the recent release of a statement from the American Statistical Association (ASA), “ASA statement on statistical significance and p-values.”³² The ASA attributes a misunderstanding and misuse of statistical significance as a contributing factor in the rise of concern about the credibility of many scientific claims. Explaining the ramifications of the ASA statement in the June 3, 2016 issue of *Science*, Goodman explains:

Bright-line thinking, coupled with attendant publication and promotion incentives, is a driver behind selective reporting: cherry-picking which analyses or experiments to report on the basis of their *P* values. This in turn corrupts science and fills the literature with claims likely to be overstated or false.³³

In 2011, EPA indicated that it will be developing a Multipollutant Science Assessment in parallel with the Integrated Science Assessments developed during the NAAQS reviews for individual pollutants. EPA also announced that it would be focusing more of its research under the multipollutant framework. However, no mention of this effort is made in the Draft Plan. Unless there is a paradigm shift, the next review will not resolve the many uncertainties that have been known for several decades.

For example, the largest multi-city study is HEI’s APHENA study which is actually a multi-continent study. While there are positive and significant combined associations for some models and for some endpoints and for some geographic areas, the overall pattern of combined associations in the large APHENA study is mixed and inconsistent. The overall pattern in various multi-city studies of PM (or any of the gases) is not what one would expect if PM health effect associations have a real physiological basis. Given the limitations of epidemiology using mass indicators, we urge CASAC and EPA to re-think the current practice of searching for the single-pollutant studies that have the strongest positive association at any lag in a city with the lowest ambient exposures. Given the stochastic variability and model selection uncertainty, this practice will identify associations that are outliers, not real effects.

The control of ambient PM (including fine PM) has been a major effort in the United States for many decades with dramatic results. Lipfert,³⁴ Darlington et al.,³⁵ and EPA³⁶ have all shown significant reductions in PM emissions and ambient concentrations (with reductions between 2 and 5 percent per year) for various time periods going back, in some cases, to the 1940s. Thus, air pollution control has been occurring in parallel with research on PM effects. The latest EPA trends for PM₁₀ and PM_{2.5} are shown below.

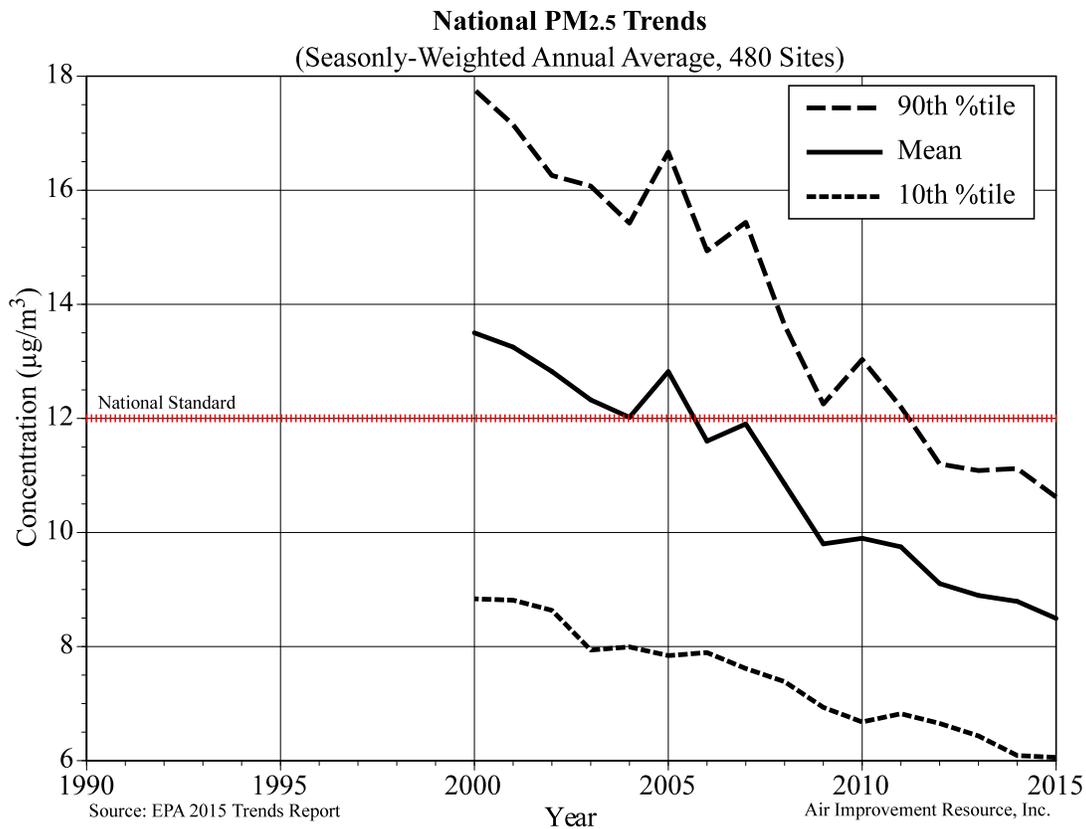
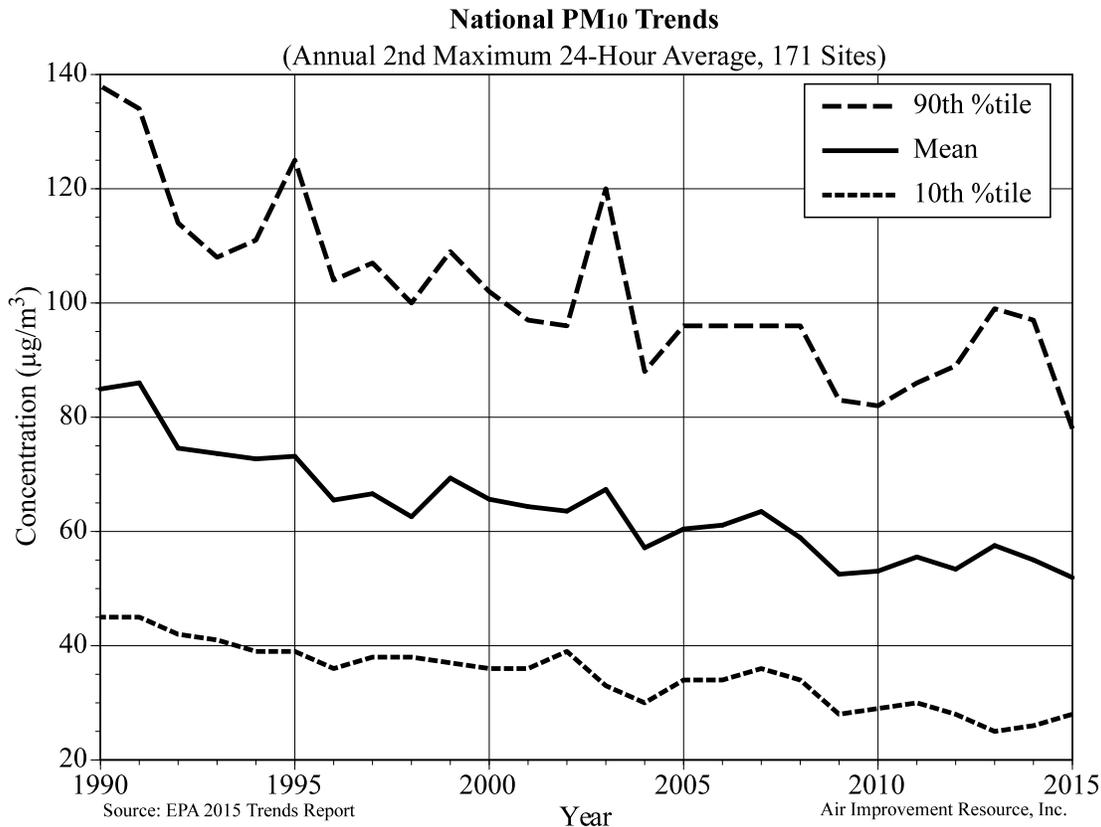
³² R.L. Wasserstein, N.A. Lazer, “The ASA’s Statement on *p*-Values: Context, Process, and Purpose. *Am. Stat.* 10.1080/00031305.2016.1154108(2016).

³³ S.N. Goodman, “Aligning statistical and scientific reasoning,” *Science*, 352:1180-1181 (2016).

³⁴ Lipfert, F. Trends in Airborne Particulate Matter in the United States; *Appl. Occup. Environ. Hyg.* 1998, 13, 370-384.

³⁵ . Darlington, T.L.; Kahlbaum, D.F.; Heuss, J.M.; Wolff, G.T. Analysis of PM₁₀ Trends in the United States from 1988 through 1995; *J. Air & Waste Manage. Assoc.* 1997, 10, 1070-1078.

³⁶ EPA’s latest trend report indicates that PM_{2.5} decreased nationally by 37 % from 2000 to 2015.



For the primary pollutant gases, CO, NO₂, and SO₂, the ambient improvements have been even greater. Hopefully, over time, based on sound science, the regulatory focus will shift from the mass of particles to the particles of greatest toxicity based on studies in which cause and effect can be reliably determined.

EPA has built a narrative around the assumed PM mortality effects that dominates the Agency's actions

Despite the major uncertainties involved in establishing PM health effects, EPA's estimated benefits from various proposed regulations are dominated by PM benefits. The Office of Management and Budget's 2013 Report to Congress³⁷ notes:

It should be clear that across the Federal government, the rules with the highest estimated benefits as well as the highest estimated costs, by far, come from the Environmental Protection Agency and in particular its Office of Air and Radiation. Specifically, EPA rules account for 58 to 80 percent of the monetized benefits and 44 to 54 percent of the monetized costs. Of these, rules that have as either a primary or significant aim to improve air quality account for 98 to 99 percent of the benefits of EPA rules.

The OMB report also indicates the large estimated benefits of EPA rules issued pursuant to the Clean Air Act are mostly attributable to the reduction in public exposure to a single air pollutant: fine particulate matter.

The report continues on to discuss the key assumptions that lead to the estimated benefits. Three are particularly relevant to the CASAC deliberations. The first is that "Inhalation of fine particles is causally associated with premature death at concentrations near those experienced by most Americans on a daily basis." The second is that "The concentration-response function for fine particles and premature mortality is approximately linear, even for concentrations below the public-health protective exposure levels established by the National Ambient Air Quality Standard (NAAQS)." The third assumption is that "All fine particles, regardless of their chemical composition, are equally potent in causing premature mortality."

It's important to note that EPA changed the benefits methodology several years ago. OMB indicates:

...it is worth noting that between FY 2001 and midway through FY 2009, all EPA's primary benefits estimates explicitly included an assumption of a threshold for premature mortality effects at lower levels—that is, health benefits were not assumed for exposure reductions below a hypothetical threshold of 10 µg/m³ (although sensitivity analyses explored alternative models). Since mid-2009,

³⁷ Office of Management and Budget, 2013 Report to Congress on the Benefits and Costs of Federal Regulations and Unfunded Mandates on State, Local, and Tribal Entities, May 2014, at pages 15-18.

EPA's primary benefits estimates reflect a no-threshold assumption.

Although this CASAC Panel is not reviewing the Agency benefits methodology that accompanies various proposed rules, the PM-mortality link (with its accompanying assumptions) has become a "narrative" that the Agency uses to justify many of its air pollution-related actions. We urge the Agency and CASAC to focus the upcoming review on key areas that address the evidence in support of and the evidence against these three key assumptions. These assumptions also undergird the Human Health Risk and Exposure Assessment (HREA) that is part of the NAAQS review so CASAC input will be critical to making judgments as to the weight that will be given to the HREA.