Dear Administrator:

The Clean Air Scientific Advisory Committee (CASAC) met on April 1-2, 2009 to review the *Integrated Science Assessment for Particulate Matter* (First External Review Draft, December 2008). In this letter, we summarize the Panel's major comments (individual comments are attached).

The Panel commends the EPA Staff for the development of a generally excellent and comprehensive first-draft PM ISA. The document draws on a massive base of evidence that is usefully summarized in tables and the appendices. The evidence is thoughtfully synthesized in a transparent fashion; the framework for classifying the strength of evidence has continued to evolve and provided transparency in documenting how determinations were made with regard to causation. Most chapters were viewed as excellent, particularly for a first-draft document. Chapter 2, which summarizes and integrates across the chapters, was thought to be an invaluable component of the ISA.

The Panel has a number of comments that expand beyond the 10 charge questions. These include:

- The ISA brings together the most recent evidence on PM and shows that PM composition has implications for health and welfare, in particular climate. We recommend that the Staff expand its synthesis to more fully address current understanding of risks to health in relation to PM size and composition, as well as the effects of PM on climate. The ISA provides an invaluable platform for assessing the current state of knowledge on these topics. We urge the addition of a synthesis on this topic to Chapter 2.

- The ISA does not sufficiently address PM and climate, both with regard to climate change and the associated health effects.

The ISA is the foundation for the REA and consequently it is the basis for justifying the selection of concentration-response relationships for use in the risk assessment. Consequently, the ISA needs to set out as clearly as possible, the concentrations at which observations have been made. This dimension of data display is currently lacking, but needs to be reflected in tables and figures.
Responses to Charge Questions:

1. **The framework for causal determination and judging the overall weight of evidence is presented in Chapter 1. Is this framework appropriately applied for this PM ISA? How might the application of the framework be improved for PM effects?**

The CASAC regards the framework for causal determination and judging the weight of evidence as presented in Chapter 1 to be appropriate. The two-step approach, using first a categorization of the evidence in support of causation and second an evaluation of exposure-response is a reasonable, logical process and is supported by CASAC. By defining the certainty with regard to the presence of causal effects, the ISA sets out a range of adverse health effects, along with an implied statement as to the likelihood of benefits following controlThe categorization gives guidance to the Administrator as to the potential for public health benefits from the PM (or other) National Ambient Air Quality Standard (NAAQS). The categorization reflects the strength of evidence and not the potential magnitude of public health benefits; those effects for which the evidence is less certain should also receive consideration in the Risk and Exposure Analysis (REA) and in policy deliberations.

Because there is concern for susceptible and vulnerable populations, the concepts of confounding and effect modification need to be sufficiently developed so that readers of the ISA understand the relevance of the concept of effect modification to consideration of susceptibility. We suggest that the topic be addressed in this chapter and then addressed more comprehensively in Chapter 8.

Publication bias is likely to be relevant in the assessment of causality, and perhaps even more so in the assessment of the evidence characterizing concentration-response relationships. Discussion is needed on the implications of publication bias; how it is detected; and how its consequences should be taken into account.

The ISA handles PM_{10}, $PM_{2.5}$, and $PM_{10-2.5}$, as though they are separate entities, even though the latter two are the components of PM_{10}. The CASAC cautions against this approach and notes that PM_{10} is a mixture that contains varying proportions of particles in the smaller and larger size ranges. The current approach leads to inconsistencies in classification of evidence with the evidence for respiratory morbidity classified as *sufficient* for $PM_{2.5}$, but likely for PM_{10}, which includes $PM_{2.5}$When possible, the particle size distribution of the PM_{10} mixture should be provided. To the extent possible, the document should take a more integrative approach in drawing inferences across the range of PM sizes. Similarly, a discussion of the relevance or importance of particle composition for the different particle size fractions is warranted.

2. **Chapter 2 presents the integrative summary and conclusions from the health effects evidence at the beginning of the ISA with the evidence characterized in detail in subsequent chapters. (Environmental and public welfare effects evidence is evaluated and summarized in Chapter 9.) Is this a useful and effective summary presentation? How does the Panel view the inclusion in Chapter 2 of only health categories with causal determinations of (a) likely to be a causal relationship or (b) a causal relationship?**

The ISA is comprehensive, lengthy, and complex. Chapters 3, 4, 5, 6, 7, and 8 are detailed and well documented, but are so extensive as reduce the functionality of the document for readers. . Consequently, the public and policy makers need the high-level summary provided in the 26 pages of Chapter 2, which provides an excellent summary of the major acute and chronic health impacts ofPM.

The CASAC PM Panel commends the inclusion of Chapter 2 and recommends similar chapters for future ISAs. Inevitably, there are conclusions which require further documentation, but one can easily find the corresponding sections of subsequent chapters. In answer to the charge question posed, we are affirmative and find it to be a "useful and effective summary presentation."

We also approve of the five-level hierarchy developed for causal determination. This is a reasonable approach to a central issue in the development of the ISAs and previously the Criteria Documents (CDs). The EPA staff has critically reviewed the relevant literature on this topic and has made specific recommendations regarding their conclusions with regard to causality. We agree with the approach of starting with a list of the key health effects and a firm statement with regard to conclusions of causality and following this by a brief description of the key findings supporting the conclusions. This approach should become a model for future ISA documents.

In general, the Panel concurs with confining the summary to evidence with causal determinations of "(a) likely to be a causal relationship or (b) a causal relationship." But it makes two recommendations. First, the summary should point the reader to appropriate sections of Chapter 1 where the definitions of the five-level hierarchy of causal determination aregiven. Second??

The Panel strongly recommends that the findings of Chapter 9 be included in this summary. Without including this material, the summary is imbalanced and does not give sufficient weight to the ecosystem and welfare effects. Additionally, the Panel recommends that the ISA should acknowledge and address the broader relationships between the ecosystem and welfare effects considered in Chapter 9 and human health. Climate change has diverse implications for human health and reduced visibility is a potential environmental stressor. We also suggest addition of a section entitled "Emerging Issues." This section could address health effects for which the evidence has not reached the top two categories of strength of evidence and point to research needs. It could address topics of likely concern in the future, such as epigenetic changes or influences of PM on premature birth and low birth weight babies. It could also highlight other topics that have been identified through the extensive review process underlying the development of the ISA.

3. To what extent are the atmospheric chemistry and air quality characterizations clearly communicated, appropriately characterized, and relevant to the review of the PM NAAQS? Does the information on atmospheric sciences and exposure provide useful context and insights for the evaluation of human health effects of PM in the ISA?

a. Is accurate and appropriate information provided regarding PM source characteristics, techniques for measuring PM and its components, policy-relevant background PM, and spatial and temporal patterns of PM concentration? Are the analyses and figures presented in Chapter 3 effective in depicting ambient PM characteristics?

Ch. 3 generally describes the relevant atmospheric chemistry, air quality characterization and exposure assessment that is relevant to the NAAQS review. The chapter was well done and the length is justified, given the new data available.

However, the section on measurement methodsneeds to be improved. There needs to be a more complete discussion of PM mass measurements and the serious limitations of the current FRM for PM. The current FRM does not provide complete and adequately time-resolved concentration data, nor does it provide an accurate indicator of mass concentration, given known losses of semivolatile constituents. There needs to be discussion of the quantification of $PM_{10-2.5}$, and a justification of the use of PM_{10} as an indicator of coarse particle exposure.

There is a lack of information on the presence of chemically reactive species associated with particles (particularly SOA and their formation by atmospheric chemistry) and of the chemical composition of coarse particles.

The emission inventory data needs to be better integrated with source apportionment results and the quantification of contributions from primary and secondary sources better described.

Changes from previous reviews in the rationale and methodology for estimating the policy relevant background should also be addressed.

b. Is the evidence relating human exposure to ambient PM and errors associated with PM exposure assessment presented clearly, succinctly, and accurately? Are there PM exposure issues that should be expanded, shortened, added or removed?

The current exposure section should be re-organized to flow more logically and revised to discuss additional PM issues. Presently, the section focuses primarily on 24hr $PM_{2.5}$ exposures and corresponding ambient concentrations. It should be modified to include discussions of shorter–term exposure (e.g., hourly) as well as exposures of longer duration (e.g., annual), and of PM_{10} and $PM_{10-2.5}$ in addition to $PM_{2.5}$. Further, the section should discuss how the relation between ambient PM and personal exposure varies under different scenarios (e.g., populations measured at single points in time andintra- or inter-community comparisons).

c. To what extent does the Panel find Annex A appropriate, adequate and effective in supporting the ISA?

The balance of data between the Chapter and Annex is good, although the Annex needs a table of contents to make it more navigable. The Panel generally appreciated the completeness of the material presented in Appendix A. Using the "search and find" approach, it does prove useful in supporting the material in Chapter 3. Annex A would be more useful if text references to it were more specific (table a-2, etc.) rather than just a generic 'see Annex A'.

4. The dosimetry of PM is discussed in Chapter 4. The primary focus is on factors that might lead to differences in deposition and clearance between individuals, species, and as a function of the physicochemical properties of particles. Is the review of basic dosimetric principles presented in sufficient detail? Are the new particle translocation data adequately and accurately described? Recognizing an overall goal of producing a clear and concise chapter, are there topics that should added or receive additional discussion? Similarly, are there topics that should be shortened or removed? To what extent does the Panel find Annex B appropriate, adequate and effective in supporting the ISA?

In general, the review of basic dosimetric principles is well written and presented in sufficient detail. It is a needed component of the ISA. Information about particle translocation is largely up to date.

There is one evident gap to be addressed. A section is needed under "4.2.4 Biologic Factors Modulating Deposition" that addresses exercise, increased ventilation, and route of breathing (nose vs. mouth). For both children and adults, exercise has a strong effect on deposition and retention and hence on dose. First, greater amounts of PM are inhaled with exercise, the amount inhaled being proportional to minute ventilation. Second, deposition mechanisms are a function of linear velocity of the inhaled air, of residence time, and of other factors related to ventilation. Third, as ventilation increases, most people switch from nose breathing to mouth breathing. The elimination of the nasal filter has a substantial impact on deposition, particularly the deposition of larger particles in the airways. For example, coarse particles, filtered by the nose under

sedentary conditions, have a greater probability of reaching the large airways and being deposited there.

The chapter also would be enriched by additional discussion of some specific PM components. What are common leachable components, and how do they differ in their clearance mechanisms? What is the fate of metals coming from soluble particles? What organs do they reach and what are the implications of retention of PM components in the brain, heart, kidneys or other critical organs?

Annex B is appropriate, adequate, and effective in supporting the dosimetry chapter.

5. **Chapter 5 is intended to support the evaluation of health effects evidence for both short-term and long-term exposures to PM. Some potential modes of action may underlie a number of health outcomes and may contribute to health effects of both short- and long-term exposures. Thus, the potential modes of action are described briefly in Chapter 5, and some specific study findings are discussed in more detail in the relevant sections of Chapters 6 or 7. What are views of the Panel on this approach and on the characterization of potential modes of action for PM-related effects in Chapter 5?**

Chapter 5 is essential to establishing a foundation for interpreting the evidence on the health risks of PM. It outlines basic mechanisms of action, and thus contributes to understanding the plausibility of the findings presented in subsequent chapters. The common fundamental toxic mechanisms, limited in number, are well described, particularly the role of reactive oxygen species (ROS). The chapter is short, focused and incorporates informative illustrations that describe the interplay of pathogenetic mechanisms.

Each section provides a clear summary of biological effects. However, it is important to establish whether these effects are similar across species and under what conditions. This could be true for paths of activation, species sensitivity and/or tolerance, gender-based differences in response.

The Panel recommends expansion of section 5.1.3 on inflammation. Inflammation is an important pervasive mechanism, and additional highlights of neutrophil biology and the inflammatory process should be delineated. There should also be a discussion of acute inflammation as well as chronic inflammation. This will undergird sections on acute responses to air pollutants (e.g. bronchoconstriction) versus responses influenced by chronic inflammation (e.g. proteolysis, emphysema, fibrosis, and other persistent anatomic changes).

The Panel notes the omission of one important mechanism—epigenetic effects of PM exposure. We recommend the addition of a new section after 5.1.10 on this topic. There is increasing evidence of PM-induced epigenetic changes in DNA, particularly DNA methylation and changes in histones. These epigenetic changes may be far more common, and probably more important

than PM-induced changes in the primary structure of DNA. Such epigenetic changes, now readily measured, can have a profound effect on gene expression and cytokine levels. There are both animal studies as well as epidemiologic studies which demonstrate significant epigenetic changes in response to PM exposure.

We welcome the section entitled gaps in knowledge. It is an excellent addition to the chapter. Other gaps could also be listed:

a. Changes in effects due to timing of exposure and timing post-exposure
b. the anatomic spatial distribution of retained particles and the implications of the distribution, e.g., airways vs. the deep lung
c. deposition, uptake and clearance of ultrafine particles**.**

6. To what extent are the discussion and integration of evidence on the health effects of PM from the animal toxicological, human clinical, and epidemiologic studies, technically sound, appropriately balanced, and clearly communicated? Does the integration of health evidence focus on the most policy-relevant studies or health findings?

d. Are the tables and figures presented in Chapters 6 and 7 appropriate, adequate and effective in advancing the interpretation of these health studies? To what extent does the Panel find Annexes C, D and E appropriate, adequate and effective in supporting the ISA?

e. In Chapters 6 and 7, toxicological studies were included in the PM ISA text if they were conducted at PM concentrations <2 mg/m^3. The toxicological focus in these chapters was on inhalation studies, with intratracheal instillation studies and in vitro studies included only if they contributed significantly to the understanding of health effects from exposure to PM. The toxicological studies excluded from the text are presented in Annex D. What are the Panel members' thoughts on this approach and the selection criteria?

Chapter 6 does a reasonable job of integrating toxicology, human clinical studies and epidemiological studies for each of the exposure scenarios discussed as well as for each of the outcomes of interest. However, the summary text sections need to be edited for consistency in approach and also to assure that the discussions are grounded and consistent with the antecedent sections that describe the evidence. For example, the discussion of short term respiratory

morbidity general conclusion seems to be contradicted with discussions of specific symptoms or pulmonary function, which does apply to all groups equally. Generally, the text relating to evidence characterization was satisfactory, but the review of details of the evidence was sometimes uneven.

There is an appropriate discussion of the time-series studies, but this section needs to have an explicit finding that the evidence supports a relationship between PM and mortality that is seen in these studies. This conclusion should be followed by the discussion of statistical methodology and the and issue of identifying threshold.

In general the tables and figures of Chapter 6 are used effectively to communicate the copious information in a succinct manner. Annexes C, D and E are thorough, appropriate, adequate and effective in supporting the goals of the PM ISA.

With the regard to the judgment of consistency of results, significant effects that move in opposite directions (HRV effects) do not necessarily imply inconsistency, but rather the lack of understanding of potential underlying mechanisms. Results presented need to incorporate specific issues of exposure, including concentration, variability of exposure and composition whenpossible composition.

As indicated in Chapter 1 on framework, discussion of the process of assigning level of causality need to be presented for each of the pollutant-outcome causality statements. Further discussion is also required for both Chapter 6 and 7 on the relation of level of causality by the PM components. Justification needs to be presented as to how PM_{10} might have a lower level of certainty than $PM_{2.5}$ (or $PM_{10-2.5}$) when PM_{10} is comprised of both.

7. **What are the views of the Panel on the conclusions drawn in the draft ISA regarding the strength, consistency, coherence and plausibility of the evidence for health effects of PM? In evaluating the evidence to draw preliminary judgments on causality, EPA carefully considered evidence from the various scientific disciplines for the PM indicators and general health or environmental effect categories. Examples of a few specific health categories are listed below that were particularly difficult in reaching a causal determination. We would appreciate CASAC comments on all of the causal determinations presented in this first draft ISA.**

    - **Short-term exposure to $PM_{2.5}$ and cardiovascular and respiratory morbidity.**
    - **Short-term exposure to $PM_{2.5}$ and mortality.**
    - **Short-term exposure to $PM_{10-2.5}$ and respiratory and cardiovascular morbidity, and mortality.**
    - **Long-term exposure to $PM_{2.5}$ and mortality**.

This chapter provides a reasonably balanced presentation of most of the outcomes of interest. However, there are several aspects of the presentation of findings that need to be addressed in the second draft. First, there needs to be care in presenting findings that come from cross-sectional studies as reflecting differences across regions and not increases in PM levels. Second, there needs to be greater balance in the presentation and discussion of study results, without undue weight being given to positive findings or characterization of estimates with CIs that include the null as "positive". This lack of balance is most evident for intermediate outcomes related to CVD. The summary statements at the end of the sections are more balanced, but the text needs to be more even. Further in the respiratory section there is a tendency to report primarily positive endpoints from studies with multiple endpoints by drawing on the individual authors interpretations of their own findings. In spite of this limitation, the overall conclusions regarding causality in the respiratory section are reasonable.

Evidence supporting a link between long-term exposure of air particle pollution to progression of intermediate cardiovascular endpoints such as surrogate measures of atherosclerosis, such as coronary artery calcium and carotid artery internal medial thickness must be interpreted in the context of the insensitivity of these methods to detect small changes in either IMT or coronary artery calcium.

Regarding the assessment of cancer mortality, particularly related to lung cancer, the Panel recommends that the cohort study findings on mortality be incorporated in the cancer incidence section rather than placing that discussion in the following section on mortality. For lung cancer, because of the poor survival, mortality and incidence are quite close. The literature search should be strengthened and better reflect the most relevant, earlier studies as well as relevant occupational studies. The section needs to better consider the plausibility of lung cancer, given the presence of known carcinogens in PM mixtures.

8. **What are the views of the Panel on the definitions of susceptibility and vulnerability in Chapter 8? Are the characteristics included within the broad susceptibility and vulnerability categories appropriate and consistent with the definitions used?**

The Committee generally supports the inclusion of the material in this chapter as part of the ISA. However, the title of the chapter is not descriptive of the content and should be revised, perhaps to "Public Health Considerations". In general, there was strong support for having synthesis material such as found in Chapter 8 to try to tie together in a succinct and policy-relevant way material presented in more detail in earlier sections. The introduction should more clearly motivate the need for ,and implications of, characterizing susceptible and vulnerable subgroups. The policy-relevance of "vulnerable" subgroups that tend to have higher exposures suggests a need to better quantify inter-individual variability, as well as spatial and temporal variability, in exposure, and to consider multiple PM sizes and components in the context of exposure. The policy-relevance of "susceptible" subgroups is that they may have different concentration-response functions than the general population or that "effect modifiers" need to be considered. The concentration-response function material would have more context if presented after the susceptibility material.

Several panelists expressed concern that the term "vulnerable" might not be the best term to use in capturing the range of population characteristics that affect the risks to health from air pollution exposure. The committee recommends that key terms be carefully defined, such as "susceptible," vulnerable," and "characteristics," and that a stronger conceptual framework be developed for understanding the implications of these factors for risks to health..

The Committee recommends that Table 8-1 be revised to be a more complete "road map" that not only lists the "characteristics" of susceptible and vulnerable groups, but that provides an indication of the weight of evidence and strength of association for each. These can be indicated qualitatively. EPA is encouraged to either further expand Table 8-1 or create additional tables that would more clearly lay-out how the "characteristics" map to health effects endpoints with respect to time frame of the effect (long-term, short-term), PM size ranges ($PM_{2.5}$, PM_{10}, PM coarse, and ultrafine), PM components of particular concern (e.g., BC, OC, EC, sulfate, and nitrate), and health effect(s) of particular concern (e.g., morbidity, mortality

The Panel recommends greater consistency in the content of Table 8-1 and the explanatory text of the chapter, and for a consistent approach to defining and using terms and "characteristics." For example, some "characteristics" are evaluating using surrogates rather than direct measurements (e.g., for socioeconomic status). Furthermore, there may be some unavoidable overlap among characteristics and between susceptible and vulnerable subpopulations. For example, socioeconomic status may be associated with conditions that lead to higher exposures (e.g., because of locations or activity patterns of the subpopulation) but also to higher susceptibility (e.g., because of health care history and pre-existing conditions). For purposes of transparency, EPA should identify and explain such overlap and the basis of a judgment to assign an issue to a particular subgroup or category.

9. How useful and complete is the scientific evidence presented and summarized in Chapter 9 regarding the effects of atmospheric PM on the environment, including (a) effects on visibility, (b) effects on individual organisms, (c) direct and indirect effects on ecosystems, (d) effects on materials, and (e) effects on climate? To what extent do the discussions and integration of evidence correctly represent and clearly communicate the state of the science?

The PM panel found that the Chapter 9 summary of welfare effects of PM (on visibility, individual organisms, ecosystems, materials, and climate) was reasonably complete and clearly written. The clarity could be improved by adding more detailed explanations of fundamental concepts like urban vs. rural visibility, and providing better definitions of acronyms and specialized technical jargon. Some of the conclusions on causality could be stated with more specificity, in ways that might provide a better indication of which effects might be most responsive to changes in PM concentrations, size fractions or chemical

components.

This added specificity would be especially useful for the section on climate effects, which would benefit from more detail on differential effects of different PM components, the relative contributions of US PM components to global aerosol and radiation budgets, and discussion of potential health effects of PM-induced climate changes.

A summary of the Chapter 9 welfare effects should be added to, and integrated with the health effects summaries in the Chapter 2 integrative overview.

The Chapter 9 discussion of visibility effects is substantially more detailed than the discussion of other public-welfare effects. To a large extent this is justified by the strong and reasonably well-understood relationship between PM concentrations and visibility impairment. However, the detail with which direct impacts on organisms and ecosystems are addressed is inadequate relative to the amount of information available and the potential importance of the issue. Important steps can be taken at this time toward causality determinations, although it is recognized that quantitative findings of causality may not be possible from available data. In the well defined process of causality determination, it is clear that the intermediate levels imply uncertainty that should drive future research to inform the next review cycle.

Chapter 9's focus on "recent" visibility information, available since the 2004 CD, relies heavily on information generated through the Regional Planning Organizations (RPO's) to support State Implementation Plans (SIPs) under EPA's Regional Haze Rule. One limitation of this is that relatively little information is provided on visibility in the suburban and urban areas, which are not protected by the Regional Haze Rule, and for which a possible secondary PM standard could provide benefits complementary to those provided by the Regional Haze Rule. Another limitation is that the PM/visibility association is described exclusively in terms of the chemical-species-specific reconstructed extinction approach that forms the basis of the Regional Haze Rule. While a similar approach could conceivably be used as an "indicator" for a secondary PM standard in urban areas, Chapter 9 could do a better job laying the groundwork for considering other potential visibility indicators, such as the relationship with sub-daily PM2.5 recommended in the last NAAQS review cycle, and the potential use of optical indicators, that might be based for example, on the combination of (size-selective) nephelometer and aethalometer measurements. Additional discussion of the strengths and limitations of the different PM and optical measurement methods and their potential use as indicators for a secondary standard would be very helpful.

Panel members also suggest that additional discussion would be useful on the importance of (and ways to include measures of) coarse particle contributions to visibility impairment which are especially important in urban areas in western states. Added discussion on the value of continuous particle size distribution measurements would be useful, as would some discussion of the importance of particle densities and differences between internally and externally mixed aerosols.

Chapter 9 includes literature citations that relate to the effects of impaired visibility on psychological wellbeing, but doesn't summarize the findings of those studies, nor does it discuss the relevance of thse findings to development of a more appropriate secondary standard different in form from the present identical primary and secondary standards for PM

10. This first external review draft PM ISA is of substantial length and reflects the copious amount of research recently conducted on PM. EPA has attempted to succinctly present and integrate the policy-relevant scientific evidence for the review of the PM NAAQS. Does the Panel have opinions on how the document can be shortened without eliminating important and necessary content?