UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

AUG 4 2009

THE ADMINISTRATOR

Dr. Jonathan Samet
Chair
Clean Air Scientific Advisory Committee
Science Advisory Board
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: Clean Air Scientific Advisory Committee's Peer Review of EPA's Integrated Science Assessment for Particulate Matter (First External Review Draft, December 2008)

Dear Dr. Samet:

Thank you for your letter about the Clean Air Scientific Advisory Committee Particulate Matter Review Panel's April 1 and 2, 2009, review of the U.S. Environmental Protection Agency's *First External Review Draft of the Integrated Science Assessment for Particulate Matter*. EPA greatly appreciates the CASAC panel's thorough review, and we are carefully considering your comments and recommendations, as well as the public comments received by the Agency, as we revise the draft ISA.

Your comments on the PM ISA, as well as recent CASAC comments on a draft Carbon Monoxide ISA, are helping us as we further develop and sharpen our approach to developing ISAs under EPA's revised process for review of the national ambient air quality standards.

A summary of our revisions in response to the CASAC comments is attached. Some of the more important changes include:

- Refocusing from an evaluation of $PM_{10}$ to an evaluation of how $PM_{10}$ results provide insights on health effects from $PM_{2.5}$ and $PM_{10-2.5}$. Separate causality determinations are no longer drawn for $PM_{10}$; however, $PM_{10}$ study results are considered in causality determinations for $PM_{2.5}$ and $PM_{10-2.5}$ where appropriate.

- Fuller discussion of the findings on health and welfare effects is included in Chapter 2 (Integrative Overview). As recommended by CASAC, the key conclusions on relationships between PM and welfare effects are included in this chapter. As noted above, the health effects conclusions focus on relationships with $PM_{2.5}$, $PM_{10-2.5}$, and ultrafine particles.

- Expanded information is provided on relationships between ambient concentrations and health effects observed in relation to short-term and long-term exposures. This includes the addition of new figures in Chapter 2 of epidemiologic study results along with some descriptive information on the air quality concentrations in the studies. In addition, to the extent possible, evidence on health outcomes reported for various PM constituents or size fractions is included in Chapters 6 and 7.

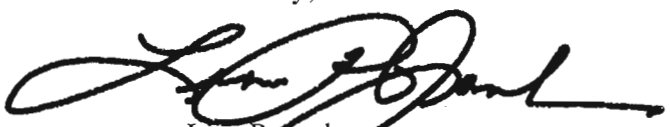
- Evaluation of the relationship between cancer and long-term PM exposure in Chapter 7 (Integrated Health Effects of Long-term PM Exposure) has been revised to consider mortality and incidence studies, as well as studies of biomarkers of exposure, in the epidemiologic section. This integration of evidence regarding cancer incidence and mortality (with most studies focusing on lung cancer) and the incorporation of results from recent studies results in a change in the causal determination for $PM_{2.5}$ from "inadequate" to "suggestive."

- The discussion in Chapter 8 is reorganized to improve the characterization of factors that may contribute to susceptibility from PM exposure.

- Expanded discussion of PM effects on visibility and climate is included in Chapter 9 (Welfare Effects), focusing on the effects of PM size fractions and components to the extent possible. The ecological effects section is reorganized to focus on types of effects, and effects of individual PM components, and additional studies are added.

Again, I thank you and the CASAC Panel members for your review of the draft ISA. Your advice and detailed comments were very valuable in guiding EPA's revisions to the draft ISA. The CASAC Panel's work will help ensure that the best science is used in informing the regulatory process.

Sincerely,



Lisa P. Jackson

cc: Holly Stallworth
CASAC PM Review Panel

**ATTACHMENT**
**Overview of Revisions in Second Draft PM ISA in Response to CASAC Peer Review Comments dated May 21, 2009**

## General Changes

An acronym was added to the front of the ISA.

When annexes or other sections were referenced in the text, they were specified (e.g., Figures A.2.1-1 through A.2.1-6 in Annex A).

New studies were added that were published on or before May 15, 2009.

## Chapter 1 – Introduction

Further detail was added on the history of the previous PM NAAQS review in Section 1.2. Section 1.3 was expanded to include more information on the process of ISA development, including study selection criteria. Section 1.5 was revised to include more specific considerations for causality determinations on PM. Additionally, consideration of publication bias was incorporated into Section 1.5.

## Chapter 2 – Integrative Overview of Health and Welfare Effects

### Sections 2.1 and 2.2: Concentrations and Sources of Atmospheric PM and Human Exposure

The text was edited to reflect the larger edits made in Chapter 3.

### Section 2.3: Health Effects

This section was reorganized to focus on the health effects evidence from studies that examined associations between morbidity and mortality and $PM_{2.5}$, $PM_{10-2.5}$, and ultrafine PM. In addition, a discussion of the evidence for health outcomes that were suggestive of an association with PM was included. At the end of the discussion of the evidence for health effects associated with short-term and long-term exposure to a specific PM size fraction, a section was added that integrates the evidence across both exposure durations, including evidence from studies that examined the mode of action, dosimetry, atmospheric chemistry, and exposure assessment. When appropriate, figures were added that summarize the overall U.S. and Canadian epidemiologic evidence for specific size fractions and exposure durations, along with the concentrations reported in the studies.

### Section 2.4: Policy-Relevant Considerations

A new section was added that includes summaries for the evidence for susceptible subpopulations, lag structure of associations in epidemiologic studies, and the PM concentration-response relationship.

**Section 2.5: Welfare Effects**
A new section was added to summarize the findings of the welfare effects chapter (Chapter 9).

**Chapter 3 – Source to Human Exposure**

**Section 3.2: Overview of Basic Aerosol Properties**
Material was added on particle morphology.

**Section 3.3: Sources, Emissions and Deposition of Primary and Secondary PM**
The sections on sources and emissions were expanded to include mobile sources (e.g., gasoline and diesel fueled vehicles). Discussion of deposition processes was moved into this section from Chapter 9.

**Section 3.4: Monitoring Issues**
The PM mass measurement section was reorganized with an emphasis on addressing $PM_{10-2.5}$ measurement techniques and performance of FRMs. The PM network and siting section was reorganized and annex tables were created to compare different monitoring networks and spatial scales for PM monitoring. A section was added on satellite determinations of surface $PM_{2.5}$. The section on measurement methods relating to climate and welfare effects was substantially increased and harmonized with the measurement section in Chapter 9.

**Section 3.5: Ambient PM Concentrations**
A brief synopsis of relevant findings from the 2004 Air Quality Criteria Document (AQCD) for PM was added to the beginning of Section 3.5. Most of the figures were updated for purposes of clarity and illustration; no additional data were incorporated into the tables or figures with the exception of PM constituent trends added to Section 3.5.2.1. All PM size-specific discussions throughout this section were rearranged into the following order: $PM_{2.5}$, $PM_{10-2.5}$, $PM_{10}$, ultrafine PM. This was done to match the order of discussion in the rest of the document and to help clarify the fact that $PM_{10}$ incorporates both $PM_{2.5}$ and $PM_{10-2.5}$. In addition, several other improvements were made to this section in response to CASAC comments including the following:

- added a summary of the findings from the PM concentration distribution tables (Tables 3.5-1 through 3.5-3)
- expanded the ultrafine particle discussion to include information on nucleation, spatial variability and chemical composition of ultrafine particles
- expanded the discussion on the statistical correlations between sites as shown in the figures and tables
- added studies looking at neighborhood scale variability and near-roadway environments;
- added a section on trends in constituents
- added a discussion on diel variability in PM constituents

**Section 3.6: Mathematical Modeling of PM (New Section)**
This section was added that incorporates receptor modeling and chemistry transport modeling (topics covered in Section 3.5 of the 1st External Review Draft) with expanded material requested by CASAC.

**Section 3.7: Background PM (Section 3.6 in 1st External Review Draft)**
More data and description were provided on current and previous methods for estimating Policy Relevant Background.

**Section 3.8: Exposure Assessment (Section 3.7 in 1st External Review Draft)**
This section was reorganized in response to CASAC comments to consolidate information related to general exposure assessment concepts, relevant studies, and the effect of exposure misclassification on epidemiologic study findings. Increased attention was given to $PM_{10-2.5}$ and ultrafine PM throughout the section. Descriptions of time-weighted microenvironmental and GIS-based models were added to the modeling subsection. Findings from the relevant studies were organized by spatial scale in part to distinguish between issues related to near road variability and issues found at the urban scale. Exposure to PM components and PM as a part of a mixture were also presented in a separate subsection. A subsection on implications of exposure assessment for epidemiologic studies was added.

## Chapter 4 – Dosimetry

**Section 4.2.4: Biological Factors Modulating Deposition**
A subsection was added to describe the multiple influences of physical activity on particle deposition. Changes in breathing route and pattern with activity level were first presented. The discussion then shifted to the effect of these alterations in breathing on total deposition fractions and dose rates. Finally, effects on tracheobronchial and apical particle deposition with exercise were presented. In the subsection on age effects, additional discussion of breathing patterns and deposition differences between adults and children was added.

**Section 4.3.1: Clearance Mechanisms and Kinetics (poorly soluble particles)**
Mucociliary clearance from the tracheobronchial airways is generally considered to be a rapid (days) process, but a portion of the particles deposited in these airways appear require considerably long periods (months) to clear. Discussion of this important phenomenon was expanded and updated.

**Section 4.3.4: Factors Modulating Clearance (poorly soluble particles)**
A new discussion on the effects of asthma, acute inflammation, and epithelial permeability on clearance was added to the subsection on respiratory disease.

**Section 4.4.1: Clearance Mechanisms and Kinetics (soluble constituents)**
The discussion of particle solubilization was expanded. Recent literature on leachable metals disposition following particle deposition was added.

## Chapter 5 – Mode of Action

The following sections were added to the chapter:

- Epigenetics (Section 5.1.11)
- Lung development (Section 5.1.12)
- Atherosclerosis (Section 5.2.3)
- Acute and chronic responses (Section 5.6)

Discussions on the following topics were expanded:

- Neutrophilic inflammation (Section 5.1.3, Section 5.1.9)
- Epithelial permeability (Section 5.1.4)
- Factors which affect resolution of inflammation/progression or exacerbation of disease (Section 5.1.9)
- Role of trigeminal nerve in CNS reflexes (Section 5.3)
- CNS plasticity (Section 5.3)
- Translocation of PM or soluble PM components (Section 5.4)
- Effects on the CNS and other systems (Section 5.5)
- Additional gaps in knowledge (Section 5.7)
- Relevant information from new studies published since the first draft and cross-referencing of all items to the appropriate sections of Chapters 6 and 7 (Section 5.7)

Paragraphs on ultrafine PM were added throughout chapter.

Where information was readily available on whether health effects are similar across species, discussions were added to the text. For example, it was noted that neurogenic inflammation may be more important in rodents than humans. However, in most cases new information was not included because literature searches failed to identify publications that elucidate these topics.

## Chapter 6 – Integrated Health Effects of Short-Term PM Exposure

For each section in Chapter 6, the causal determination for $PM_{10}$ was removed, and evidence for health effects associated with $PM_{10}$ was used to support the associations with $PM_{2.5}$ and/or $PM_{10-2.5}$ where possible and appropriate. The discussion of cause-specific mortality has been incorporated in sections on cardiovascular and respiratory morbidity, as was done for lung cancer incidence and mortality and considered in drawing causal determinations for cardiovascular and respiratory effects.

### Section 6.1: Introduction

The introduction was updated to reflect the changes made throughout Chapter 6. The section on methodological considerations was separated and moved to various sections of Chapter 1.

### Section 6.2: Cardiovascular Effects

Controlled human exposure and toxicological studies were reorganized by particle type or source (e.g., CAPs, diesel, gasoline, model particles, etc.) and subheadings were added. Intratracheal instillation studies were contained in their own subsection where applicable within the toxicology sections. The summary sections were revised and condensed by removing specific outcome headings and presenting the previous findings followed by new evidence in a more integrated fashion. The causal determinations for $PM_{10-2.5}$ and ultrafine particles were changed from inadequate to suggestive, whereas the causal determination for $PM_{2.5}$ remained unchanged from the 1st ERD.

### Section 6.3: Respiratory Effects

The figures in Section 6.3.1 were revised to include the results for all PM size fractions as opposed to $PM_{2.5}$ alone. Controlled human exposure and toxicological studies were reorganized

by particle type or source (e.g., CAPs, diesel, gasoline, model particles, etc.) and subheadings were added. Intratracheal instillation studies were contained in their own subsection where applicable within the toxicology sections. New epidemiology sections on allergic responses (Section 6.3.6.1) and host defense (Section 6.3.7.1) were added for the 2nd ERD. The summary sections were revised and condensed by removing specific outcome headings and presenting the previous findings followed by new evidence in a more integrated fashion. The causal determination for ultrafine particles was changed from inadequate to suggestive, whereas the causal determinations for $PM_{2.5}$ and $PM_{10-2.5}$ remained unchanged from the 1st ERD.

**Section 6.4: Central Nervous System Effects**
A new epidemiology section was added that summarized new studies. Toxicological studies were reorganized by particle type or source (e.g., CAPs, diesel, gasoline, model particles, etc.) and subheadings were added.

**Section 6.5: Mortality**
Along with incorporation of recent study findings, ancillary data (i.e., empirical Bayes-adjusted city-specific estimates and ambient PM concentrations) were included from Zanobetti and Schwartz (2009) for $PM_{2.5}$ and $PM_{10-2.5}$.

**Section 6.6: Attribution of Health Effects to Specific Constituents or Sources**
Individual tables for epidemiologic, controlled human exposure, and toxicological studies were moved to Annex F. The table that was formerly in Chapter 2 (Table 2-1 in the 1st ERD) was moved to this section, and includes studies from all three disciplines grouped by source category (e.g., crustal/soil/road dust, traffic, oil combustion, etc.). A new summary was drafted that includes paragraphs by health outcome (i.e., cardiovascular effects, respiratory effects, and mortality) for the different PM source categories and constituents.

## Chapter 7 – Long Term Exposure and Health Effects

For each section in Chapter 7, the causal determination for $PM_{10}$ was removed, and evidence for health effects associated with $PM_{10}$ was used to support the associations with $PM_{2.5}$ and/or $PM_{10-2.5}$ where possible and appropriate. The discussion of cause-specific mortality has been incorporated in sections on cardiovascular and respiratory morbidity, as was done for lung cancer incidence and mortality and considered in drawing causal determinations for cardiovascular and respiratory effects.

**Section 7.2: Cardiovascular Effects**
The text was edited to balance the discussion of the intermediate cardiovascular outcomes so that this line of evidence was consistent with the summary sections. Text was added to the 2nd ERD to relate chronic cardiovascular health impacts with acute cardiovascular health impacts. Toxicological studies were separated by exposure atmosphere (e.g., CAPS, ambient air, wood smoke, diesel, etc.) and intratracheal instillation studies were contained in their own subsection. Consideration of evidence on cardiovascular mortality resulted in revision of the causal determination from "likely causal" to "causal."

**Section 7.3: Respiratory Effects**
The text in this section was revised to more clearly differentiate between cross-sectional and cohort study designs. Additionally, the text was revised to ensure that the studies were characterized in a balanced and objective manner. The epidemiology sections on allergic response (Section 7.3.6.1) and host defense (Section 7.3.7.1) were expanded.

**Section 7.4: Reproductive and Developmental Outcomes**
Several new epidemiologic studies were added to this section in the 2nd ERD. The tables and figures in this section were updated to include the newly identified studies.

**Section 7.5: Cancer**
This section was revised to include the results of epidemiologic studies examining lung cancer mortality and PM concentration. In the 1st ERD this section was limited to epidemiologic studies that focused on cancer incidence. Rates of lung cancer incidence and mortality are similar, and therefore the cancer section was expanded to include studies of lung cancer mortality. A new table (Table 7-7) was included that shows the effect estimates from lung cancer incidence and mortality studies reviewed in the 2nd ERD as well as those reviewed in previous PM AQCDs. The inclusion of evidence for mortality due to lung cancer associated with $PM_{2.5}$ concentrations strengthened the causal determination substantially.

The section was also revised to include evidence from animal toxicological studies that has been accumulating for several decades on the mutagenicity and carcinogenicity of PM in the ambient air. The majority of these toxicological studies were conducted using intratracheal instillation or dermal routes of exposure. Generally, the toxicological evidence reviewed in the rest of the ISA was limited to inhalation studies conducted at PM concentrations <2 $mg/m^3$. For the 2nd ERD, toxicological studies conducted at higher concentrations and using various routes of exposure were cited in order to accurately characterize the role of PM in mutagenicity, tumorogenicity, and carcinogenicity. The toxicology section was reorganized such that mutagenicity and genotoxicity studies are described first, followed by the carcinogenesis studies. Additionally, the toxicology section has new subheadings within each section for particle or source type, which is consistent with toxicology sections for other health outcomes. This evidence included brief summaries of relevant IARC and EPA documents on diesel exhaust, as well as reviews from the peer-reviewed literature.

Also, a few recent studies examining the association between $PM_{2.5}$ and epigenetic changes were added to the end of the section. As a result of revisions to this section, the causal determination for $PM_{2.5}$ and cancer was changed from inadequate to suggestive. The causal determination for $PM_{10-2.5}$ and cancer remained unchanged (i.e., inadequate) from the 1st ERD.

**Section 7.6: Mortality**
Several new epidemiologic studies were added to this section in the 2nd ERD, most notably the results of the HEI report of the reanalysis of the ACS cohort by Krewski et al. (2009). The tables and figures in this section were updated to include the newly identified studies.

## Chapter 8 – Susceptible Subpopulations

**Section 8.1: Potentially Susceptible Subpopulations**
The definition of a susceptible subpopulation was clarified based on a workshop report from The American Lung Association (2001). A discussion on effect modification was included. The table that was originally in this section was edited to reflect the susceptibility factors examined in the health effects literature that were subsequently discussed in this chapter. The table was also revised to include the different exposure durations (short- and long-term) and PM size fractions evaluated in the studies presented in the chapter.

**Sections 8.1.1 through 8.1.7**
The remaining sections of this chapter were reorganized to more accurately reflect the exposure durations and size fractions where the evidence lies. The susceptibility factors originally included in the chapter were reconsidered and some were no longer characterized as susceptibility factors (e.g., air conditioning use and geographic location) and thus, were no longer discussed.

**Section 8.1.8**
A new section was included that summarizes the findings from all of the studies evaluated in this chapter.

## Chapter 9 – Welfare Effects

**Section 9.2: Effects on Visibility**
As recommended by CASAC, a new section on *Direct Optical Measurements* (9.2.2.3.) was added. To enhance the discussion of sense of well being as it relates to urban air quality, Section 9.2.2.4. *Value of Good Visual Air Quality* was added. Key points of these new sections were also included in the summaries in both Chapter 9 and Chapter 2. Several figures were also revised for clarity and consistency.

**Section 9.3: Effects on Climate**
The section on aerosol effects on climate was substantially increased with more details from recent publications. Specific effects from PM components and size fractions were described in more detail. In addition, more detail was added to the summary section and carried through to the summary in Chapter 2.

**Section 9.4: Ecological Effects**
This section was reorganized to focus on types of effects (i.e., direct and indirect effects) and effects of individual PM components (i.e., metals and organics). Deposition of PM specifically related to ecosystems was merged into this section while more detailed information on deposition processes was moved to Chapter 3. The causal determination was revised from causal to likely to be causal. Additionally, the introduction to the section was revised to include key conclusions from the recent $NO_X$-$SO_X$ ISA (December 2008).