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

OCT 18 2011

THE ADMINISTRATOR

Jonathan M. Samet, M.D.
Chairman
Clean Air Scientific Advisory Committee
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, D.C. 20460

Dear Dr. Samet:

Thank you for your August 10, 2011, letter providing the Clean Air Scientific Advisory Committee Ozone Review Panel's comments on the U.S. Environmental Protection Agency's *Integrated Science Assessment for Ozone and Related Photochemical Oxidants,* March 2011. We at the EPA greatly appreciate the panel's thorough review and constructive comments.

My staff carefully considered your comments and recommendations, as well as the comments we received from members of the public. The EPA's revisions address both consensus and individual CASAC comments and also incorporate findings of additional studies published through July 2011. An overview of the major revisions in the Second External Review Draft of the Integrated Science Assessment is attached. Some of the key changes made in response to the CASAC comments are highlighted below.

The CASAC panel offered a number of recommendations to enhance the organization and presentation of the evidence in the ISA. In response, we added a preamble, a preface and an executive summary. The preamble is applicable to all ISAs and includes the more general sections on ISA development and the causality framework from chapter 2. The preface includes sections on legislative background and the history of previous reviews. The material originally included in chapter 1 was moved and replaced by the executive summary. Chapters 1 and 2 were reorganized and revised to reduce redundancy and increase focus on integrative discussions.

Chapter 2 is now the first substantive chapter of the ISA. Revisions to chapter 2 include streamlining or eliminating summary materials from the subsequent chapters and expanding the integrative synthesis sections. The introductory sections specific to this ISA were placed at the beginning of chapter 2. The intent was to bring the integrative overview discussion forward in the document to make it more accessible to the reader.

The CASAC panel and public commenters expressed a need for the most current estimates of Policy Relevant Background concentrations to be included in the ISA for subsequent use in the risk assessment. The results from two important studies addressing background ozone concentrations have been added to chapter 3. Results of the EPA's modeling efforts related to PRB have also been incorporated in an appendix.

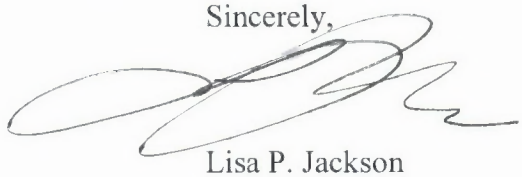
Chapter 5 was reorganized to improve the continuity of discussion between the dosimetry and mode-of-action sections. In addition, revisions were made throughout the mode-of-action sections to more clearly focus on mechanistic information that provides a background for subsequent health effects chapters, while also increasing linkage between the mechanistic discussions and effects-related discussions in chapters 6 and 7.

In chapters 6 and 7, references to and incorporation of information from previous assessments were expanded so that the evaluation of new health evidence is more clearly integrated with the substantial existing body of evidence on ozone-related health effects.

The CASAC panel's advice on the use of a broad definition of "susceptibility" has been carefully considered. We reorganized and refined discussion at the beginning of chapter 8 on the situations that can result in increased risk of ozone-related health effects. Since terms such as susceptibility and vulnerability have been used in various ways in the literature, we have used the term "at-risk" where an overarching term is appropriate and have refined discussion of individual factors.

We recognize that our efforts to protect the environment can only be as good as the science on which they are based. Independent critical reviews such as yours help to ensure that we use the best science to protect public health and our nation's environment. Please accept my appreciation for your hard work and thoughtful review.

Sincerely,



Lisa P. Jackson

Attachment

cc: Paul Anastas
James Brown
Becki Clark
Mary Ross
John Vandenberg

ATTACHMENT

Overview of Revisions in Second Draft Ozone ISA in Response to CASAC Peer Review Comments dated August 10, 2011

Chapter 1 – Introduction

An Executive Summary has been prepared and replaces Chapter 1. As part the document restructuring, Chapter 1 materials have been revised and moved, specifically:

a) the more general sections on the development of the ISA and the causality framework are being placed in a Preamble that can support all ISAs;
b) the introductory sections specific to this ISA are placed at the beginning of Chapter 2; and
c) sections on legislative background and history of previous reviews is being moved to a Preface in the front matter of the ISA.

Throughout the document, the editorial suggestions provided by individual CASAC members were reviewed and considered in developing the second external review draft.

Chapter 2 – Integrative Health and Welfare Effects Overview

Generally, the chapter was revised to eliminate redundancy and make it more concise. Efforts were also made to provide a narrative discussion that clearly communicates the most important information from the ISA to non-subject matter experts.

Sections 2.1 and 2.2 incorporated material originally in Chapter 1.

Chapter 3 – Atmospheric Chemistry and Ambient Concentrations

Section 3.2
Information was added on O_3 sources and chemistry in indoor air.

Section 3.4
The results were added from two important studies addressing background O_3 concentrations and incorporated material in an appendix (**Section 3.10, Appendix C**) from EPA modeling efforts on related topics.

Section 3.5
The text was updated to reflect current monitoring protocols and network capabilities, including the updated status of the NCore network. Figures throughout this section are now easier to interpret.

Section 3.6
All figures and tables were updated to include all finalized and verified 2009 data from AQS.

Section 3.7
A summary section for Chapter 3 was added.

Section 3.8, Appendix A
The figures presenting policy relevant background were updated to reflect new results published since the first draft was released.

Section 3.9, Appendix B
The appendix's length was reduced by condensing figures.

Chapter 4 – Exposure to Ambient Ozone

Section 4.3, Exposure Measurement
Tables were prepared that summarize data from studies of indoor-outdoor and personal-ambient ratios and correlations.

Section 4.4, Exposure-Related Metrics
A new section was developed to organize material on parameters relevant to exposure estimation. Added material on evidence of averting behavior on high-O_3 days, which would tend to reduce O_3 exposure.

Section 4.5, Exposure Modeling
A table was prepared that summarizes strengths and limitations of exposure modeling approaches. Information was added on exposure model applications. A subsection was added on air exchange rate modeling.

Section 4.6, Implications for Epidemiologic Studies
The discussion of the relevance of central-site monitoring data for epidemiologic studies based on evidence from personal exposure studies, including potential uncertainty and bias due to exposure error, was improved. Material was added on the effect of averting behavior on epidemiologic results.

Section 4.7, Summary and Conclusions
The summary section was revised to be more concise and focused on the main findings of the chapter, particularly with regard to their implications for interpretation of epidemiologic studies.

Chapter 5 – Dosimetry and Mode of Action

The chapter was reorganized in response to CASAC comments by first describing O_3 dosimetry (**Section 5.2**), followed by the formation of reactive products (**Section 5.2.3**), then the role of these products in the modes of action of O_3 (**Section 5.3**), and finally inter-individual variability (**Section 5.4**) and species homology (**Section 5.5**). An introduction was added to present the organization for the chapter and to describe the connection between the dosimetry and modes of action of O_3. The rationale for including mode of action in Chapter 5 rather than in later chapters was included in the chapter introduction (**Section 5.1**). Throughout all sections, discussion of studies published after 2006 and those included in previous AQCDs were integrated.

Section 5.2: Human and Animal Ozone Dosimetry
Language describing respiratory tract regions was harmonized and an illustrative figure was included. Material was added on the gas transport principles (**Section 5.2.2.1**). Sections describing the target sites for O_3 dose (**Section 5.2.2.2**), inter-individual variability in dose (**Section 5.2.2.6**), and physical activity (**Section 5.2.2.7**) were expanded in response to CASAC comments. The two sections focusing on secondary reaction products from the first ERD were merged into one discussion focusing on the formation of reaction products.

Section 5.3: Possible Pathways/Modes of Action
This section was reorganized to deemphasize effects and increase emphasis on toxicity pathways and key events involved in the modes of action (terms introduced in **Section 5.3.1**). Accordingly, Figure 5-6 from the first ERD was replaced with a new figure (Figure 5-9). The revised Chapter 5 contains more linkages to the relevant sections of Chapters 6 and 7. Also, **Section 5.3.1** states a deliberate emphasis on more recent studies and on studies in humans that inform biological mechanisms. Nonetheless, older research and research in animal models that inform biological mechanisms were included in Chapter 5. Discussion of the extrapulmonary effects of ozone and the overall summary were expanded.

Section 5.4: Inter-individual Variability in Response
This section was reorganized to include both dosimetric and mechanistic considerations. Discussion of asthma and allergic airways disease, as a pre-existing disease and condition, was moved to **Section 5.4.2.2**. Discussion of obesity as a pre-existing condition (**Section 5.4.2.2**) has been expanded. Discussion of adaptation has been revised to focus on the attenuation of responses (**Section 5.4.2.5**). Interpretation of studies measuring markers of inflammation following multi-day exposures has been clarified. A new figure has been added to this section (Figure 5-10).

Section 5.5: Species Homology and Interspecies Sensitivity
This section was expanded in response to CASAC comments. New figures were included comparing tissue dose distributions for O_3 in humans and experimental animal species.

Section 5.6: Chapter Summary
An overall chapter summary was included to highlight the connection between O_3 dosimetry, including the formation of secondary oxidation products, and the role of reaction products in the mode of action of O_3. The point was made that the majority of the key events discussed in **Section 5.3** have been demonstrated in both animals and human subjects in response to ozone.

Chapter 6 – Integrated Health Effects of Short-Term Ozone Exposure

In the previous draft, the words tolerance, adaptation, and attenuation were used frequently and sometimes interchangeably. Revisions were made to use these terms when appropriate and within a consistent context throughout the chapter.

Section 6.2, Respiratory Effects
Each plot summarizing the epidemiologic evidence for lung function and biological markers of airway inflammation displays results for a single parameter (e.g., FEV_1) or biological marker (e.g., eNO) within the section. This was done in the interest of clarity. Also to improve comparability among studies, where data are available, results are presented as the percent change in an endpoint per standardized increment in ambient O_3 exposure. Within toxicological and controlled human exposure sections that focused on respiratory effects, specific study descriptions were revised as requested, and references to relevant studies or tables from the 1996 and 2006 O_3 AQCDs were included as appropriate. Additional discussion was added regarding the experimental design of controlled human exposure studies as well as effects observed during exposure to filtered air. A table was also added describing key morphometric studies.

Section 6.3, Cardiovascular Effects
Consistent with the respiratory effects section, where appropriate, tables of toxicological study details were added and specific study details were removed from the text.

Section 6.4, Central Nervous System Effects
This section was re-written and a table was added for clarity and a more conceptual focus. Descriptions of older studies were added along with a reference to the appropriate table of toxicology studies from the 1996 O_3 AQCD.

Chapter 7 – Integrated Health Effects of Long-Term Ozone Exposure

The duration term for long-term studies is stated at the beginning of the chapter. Efforts were made to clearly identify exposure periods in the text and tables. With the exception of birth outcomes, most discussions of acute exposure studies have been removed. Revisions were made to use the terms adaptation, tolerance, or attenuation with greater consistency. Other wording choices, such as 'seasonal' have also been revisited.

Section 7.2.3.1, Pulmonary Structure and Function, Toxicology
A table has been added and additions to the text made to include key toxicological studies of respiratory effects, regardless of publication date.

Section 7.4, Reproductive and Developmental Effects
A table of key reproductive and developmental toxicological studies (including older studies) was added.

Section 7.5, Central Nervous System Effects
This section was rewritten and a table added for clarity and a more conceptual focus.

Section 7.6, Carcinogenic and Genotoxic Potential of Ozone
Older toxicological studies were revisited and the text revised to accurately reflect study findings. References to relevant tables of toxicological studies in the 1996 O_3 AQCD were added where appropriate.

Section 7.8, Overall Summary
This section was added along with a table summarizing all of the causal determinations from the chapter.

Chapter 8 – Population Susceptible to Ozone-Related Health Effects

Recognizing potential confusion in the use of the term "susceptible" to encompass factors that increase potential for risk of O_3-related effects, Chapter 8 introduces the term "at risk" where an overarching term is appropriate. The introduction to the chapter has been revised with expanded discussion on how individuals could experience increased risk for O_3-related health effects, utilizing the terms identified in by the CASAC panel (i.e. intrinsic, extrinsic, increased dose, greater exposure). These terms are used throughout the chapter, as appropriate, in characterizing the factors that may lead to increased risk.

A new section has been added to expand discussion of exercise and dose, titled "Heightened Exposure," that addresses difference in exposure due to outdoor work or use of air conditioning. Information on how exercise may affect O_3-related health effects is also integrated into other parts of the chapter. For example, this applies in the section on children, as they spend more time outside and are more active than adults.

Information on important genes, dietary factors, as well as other supporting toxicological literature has been added to the chapter.
Finally, the discussion of older age groups has been clarified to state that the strongest evidence for increased risk with O_3 exposure is for mortality. This has been carried through the section and chapter summaries.

Chapter 9 – Environmental Effects: Ozone Effects on Vegetation and Ecosystems

Chapter 9 has been reorganized to lessen the repetition among the sections. As suggested by CASAC, the discussion of effects was consolidated into fewer, but more integrated sections.

Section 9.4, Nature of Effects on Vegetation and Ecosystems
The definition of ecosystem was refined to include a discussion of ecosystem boundaries and incorporate the concepts of physical exchange and the biotic and abiotic interactions among ecosystem components. More discussion and interpretation of modeling approaches were added to **Section 9.4.3**. Information and consideration of O_3 impacts on stomatal conductance and ramifications at various scales have been consolidated in **Section 9.4.5** (Water Cycling).

Chapter 10 – The Role of Tropospheric Ozone in Climate Change and UV-B Effects

Recent studies addressing O_3 and climate were added, including several on trends (**Section 10.2**). Figure 10-1 was revised to reflect additional steps in the role of ozone in climate change. **Section 10.2.4** was expanded on the competing effects of ozone precursors on climate. Figure 10-4 was added showing time series of O_3 precursors in comparison to long-lived greenhouse gases predicted using four Representative Concentration Pathways scenarios. **Section 10.2.6.3** was added on the impact of 21st century climate on tropospheric O_3.

Section 10.3
A study was added describing catalysis of trace metals including mercury resulting from UV-B exposure.

Section 10.4
A summary section was added for Chapter 10.