UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

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March 13, 2012

EPA-CASAC-12-004

The Honorable Lisa P. Jackson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Subject: CASAC Review of the EPA's *Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Second External Review Draft – September 2011)*

Dear Administrator Jackson:

The Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel met on January 9 - 10, 2012, to peer review the EPA's *Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Second External Review Draft – September 2011),* hereafter referred to as, the ISA. The CASAC's consensus responses to the agency's charge questions and the individual review comments from the CASAC Ozone Review Panel are enclosed. The CASAC's key points are highlighted below.

The CASAC commends EPA for substantial revisions to the first draft ISA based upon its prior advice (August 2011). Nevertheless, the CASAC has further recommendations for improving the document and recommends that EPA develop a third draft of the ISA and provide it to the CASAC for a review focused on the key changes called for in this letter.

Preamble, Preface, Executive Summary, and Integrative Overview

The CASAC appreciates the inclusion of discussions of the ISA development process and the framework for evaluation of evidence for causal determination in the Preamble. The CASAC recommends that ISAs for other criteria pollutants include the content and structure of the Preamble. The CASAC supports the inclusion of historical aspects of ozone regulation in the Preface, although the CASAC notes several omissions related to recent decisions; the history should be updated to cover the September 2011 decision to not move forward with the reconsideration of the 2008 National Ambient Air Quality Standard (NAAQS) for ozone. The Executive Summary is informative and accurate, but the language should be simplified to a level appropriate for a non-technical audience. The Integrative Overview should reflect its title and provide a thoughtful synthesis and integration of the scientific evidence covered in the chapters of the ISA. This type of synthesis is critical to the purpose of the ISA.

Atmospheric Chemistry and Ambient Concentrations

Chapter 3 provides a thorough overview of the atmospheric chemistry relevant to ozone pollution, the ability of models to describe it, and the ozone concentration patterns over the United States, with particular attention to the background concentration. However, the connection of this material to its eventual utilization in the Risk and Exposure Assessment (REA) and the Policy Assessment (PA) needs to be improved. There should be a more explicit discussion of how the topics emphasized relate to the needs of the analyses planned for these documents, along with a more complete characterization of relevant uncertainties. In particular, the discussion of background ozone concentration needs a stronger synthesis of current knowledge along with a quantitative assessment of the related uncertainties.

The chapter is thorough and well-informed. However, there are deficiencies in the chapter that need to be addressed. Three new studies on background ozone (McDonald-Buller et al., 2011; Emery et al., 2012; Lin et al., 2012) should be discussed as they offer a much-needed resource for estimating uncertainties in the background ozone concentrations computed with GEOS-Chem. More emphasis needs to be placed on background estimates relevant to the fourth-highest maximum daily 8-hour average ozone concentrations. The discussion needs to acknowledge the limitations of models in capturing the high extremes of the ozone distribution in remote sites. Long-term trends in ozone levels over the United States warrant more consideration in the ISA. More discussion of the western oil/gas field ozone scenario may be helpful, along with consideration of the value of satellite observations for ozone and its precursors.

Exposure to Ambient Ozone

Chapter 4 has been significantly improved in terms of its content, organization, and scientific accuracy. Nonetheless, the CASAC has several recommendations for improving this chapter. First, a discussion of long-term ozone exposures should be included, covering how they relate to corresponding long-term ambient ozone concentrations and addressing the potential for confounding in epidemiological studies by co-pollutants. Second, discussions on the results from personal exposure simulations at several different NAAQS level scenarios should be reconsidered or deleted, as the findings of geographic variability in the 8-hour ozone exposures of children are not supported by the data. Moreover, this type of discussion may be more appropriate for the REA. Third, the analysis of population proximity to ozone monitors should be tied to maps of ozone concentrations, where ozone concentration and population data are presented together in the same analysis of monitor proximity. Fourth, findings from exposure studies should be integrated with discussions in other chapters of the ISA, as topics related to exposure error, confounding, and highly exposed populations are potentially important for the REA and PA.

Dosimetry and Mode of Action

There have been numerous improvements in the organization and content of Chapter 5, but further improvement is needed. Early in the chapter, there should be a listing and definition of the various dose metrics and these definitions should be used consistently throughout the chapter. In addition, the connection between dosimetry principles and theoretical or experimental observations of dose distribution and tissue damage should be discussed with greater clarity and detail. There should be a better discussion on the underlying assumptions and computations to support whether adverse responses result from exposure to ozone alone or from reactions of toxic products of ozone with endogenous

substrates. The discussion on exercise could be better linked to dose-response considerations in Chapters 6 and 7 by defining specific activity levels in terms of relevant ventilatory conditions. The revised chapter should provide a solid foundation for understanding the relationships among exposure, dose, and effects observed in animal toxicology and human health studies. There needs to be better integration within the sections of this chapter as well as with the other chapters of the document.

Integrated Health Effects of Short- and Long-Term Ozone Exposure

Chapters 6 and 7 have been substantially improved since the first ISA draft, particularly the organization, the figure legends, and the expanded text describing the studies. However, the CASAC notes several areas of the chapter that can be further improved. Although the intent to make the ISA more concise is appreciated, the document should clarify whether studies conducted since the 2006 Ozone Air Quality Criteria Document (AQCD) make a critical advance in the strength of evidence and their findings should be presented in the context of the previous studies. Not all previous studies need to be discussed, but the key studies that still are critical elements of the overall evidence foundation should be incorporated. In the CASAC's opinion, the evidence from toxicological, human clinical, and epidemiological studies of short-term ozone exposure all support upgrading the causal determination for cardiovascular effects from "suggestive of a causal relationship" to "likely to be causal relationship." Moreover, this classification would be consistent with the "likely to be causal relationship" determination for cardiovascular-related mortality. EPA should give consideration to the totality of the evidence on cardiovascular effects in making this determination.

Populations Potentially at Increased Risk for Ozone-Related Health Effects

Additional revisions would further strengthen Chapter 8, which has been improved in this second draft. With regard to conceptual and definitional issues, it is important for this chapter to clearly distinguish two broad processes that can place populations at "increased risk": (1) greater ambient exposure and/or greater internal dose and (2) greater adverse health effects given a specific dose. The term "populations-at risk" as defined in the preamble and used in Chapter 8 appears to encompass both processes but this distinction could be clearer and further developed. The term "populations-at-risk" is useful for the REA and PA. If the terms "sensitive, vulnerable, or susceptible" populations are used in the document, they need to be clearly defined. The distinction between both processes should also be carried through in the review of the evidence.

With regard to the review of the evidence, diverse studies are covered but without sufficient synthesis of the evidence. Additional synthesis highlighting the key conclusions that can be drawn from the studies would be helpful. There also needs to be an enhanced discussion of the methodological challenges inherent in studying modifiers of ozone effects. Key among these are inconsistencies in the measures of the effect modifiers studied and inadequate sample sizes in the various cross-classified categories. These methodological issues may explain some of the differing findings observed across studies.

Environmental Effects: Ozone Effects on Vegetation and Ecosystems

The EPA has responded appropriately to the issues identified by the CASAC in the first draft ISA regarding ozone effects on vegetation and ecosystems. Chapter 9 adequately summarizes the current state of knowledge of ozone effects and incorporates new information (since the 2006 Ozone AQCD) on the molecular and genetic underpinnings of ozone impacts, on available comparisons of chamber-based

and more recently published non-chamber exposure studies, along with the results of several meta-analyses that provide an integration of the previously available information. It also adequately summarizes the results of a series of ecosystem models that examine the effects of ozone on aspects of productivity. To improve the chapter, the CASAC recommends: adding a table of causal determinations, additional technical editing, and adding definitions and explanations of terms. Several areas need revision, including the reference to "sensing of ozone" by plants, which does not describe the process as currently understood; the lack of clear, unambiguous statements regarding the impact of ozone on root growth; and the lack of emphasis on ambient ozone effects on native vegetation. Further, the effect of ozone on water loss by plants (specifically, the potential for a decrease as well as a potential increase in water loss due to sluggish stomata) should be incorporated into the discussion and overarching figures.

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

Discussion of ozone as a climate-relevant gas is appropriate, in view of the need for concerted climate-air quality regulatory objectives in the future. Consideration of ultraviolet B (UV-B) effects is also appropriate, although these appear to be very small. The chapter acceptably delivers on these two topics but revisions are needed in several areas. Projections for future global emissions of ozone precursors in the ISA are based on the Special Report on Emissions Scenarios (SRES) of the Intergovernmental Panel on Climate Change (IPCC) Third Assessment Report (TAR) (2001) but these have now been superseded by the IPCC Fifth Assessment Report (AR5) Representative Concentration Pathways (RCP) scenarios. Even though there is a need to discuss the SRES scenarios because they have been used in most studies reported so far, the ISA should inform readers on the new RCP scenarios that will be used in the future. The consideration of radiative forcing from ozone precursor emissions is inadequate and the CASAC offers specific recommendations for improvements. The discussion of UV-B effects needs to be improved by more succinctly stating that the effect of expected tropospheric ozone changes on UV-B radiation is quite small and provide a quantitative upper limit on the effect. Similar to prior chapters, bolded statements of causal determination should be made in the chapter, and the text supporting those determinations needs to be consistent. A table of causal determinations also should be provided.

The CASAC appreciates the opportunity to provide advice on this issue and looks forward to reviewing the third draft of the ISA.

Sincerely,

/Signed/

Dr. Jonathan M. Samet, Chair
Clean Air Scientific Advisory Committee

Enclosures

NOTICE

This report has been written as part of the activities of the EPA's Clean Air Scientific Advisory Committee (CASAC), a federal advisory committee independently chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC provides balanced, expert assessment of scientific matters related to issues and problems facing the agency. This report has not been reviewed for approval by the agency and, hence, the contents of this report do not necessarily represent the views and policies of the EPA, nor of other agencies within the Executive Branch of the federal government. In addition, any mention of trade names or commercial products does not constitute a recommendation for use. The CASAC reports are posted on the EPA website at: http://www.epa.gov/casac.

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Consensus Responses to Charge Questions on
EPA's Integrated Science Assessment for
Ozone and Related Photochemical Oxidants
(Second External Review Draft – September 2011)

Preface, Preamble, Chapters 1 (Executive Summary) and 2 (Integrative Overview)

The CASAC panel offered a number of recommendations to enhance the organization and presentation of the evidence in the ISA. An Executive Summary has been prepared and is put in the place of Chapter 1. As part of the development of the Executive Summary and restructuring of the integrative overview chapter, 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 are contained in a Preface in the front matter of the ISA. The intent was to bring the integrative overview discussion to the front of the document, thus making it more accessible to the reader.

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy of these summary sections and the conclusions therein.

The CASAC expresses appreciation for the major revisions that have been made in this second draft of the ISA, particularly the new Preamble, Preface, and Chapter 1 (Executive Summary), as well as revisions made to Chapter 2 (Integrative Overview).

Preamble

The CASAC applauds the new Preamble, which not only supports this ISA, but should be incorporated in other ISAs as well. Greater uniformity and clarity among the various documents related to the National Ambient Air Quality Standards (NAAQS) will be helpful to the Agency, to the CASAC, and to the public. In addition, the CASAC suggests that the Preamble be submitted to an appropriate journal for peer review and publication with recognition of its authors. Alternatively, a free-standing Preamble can be adopted by the EPA and reviewed by the CASAC. Its substance and its future use are too important for it to be overlooked as simply part of this larger and not widely circulated document.

The CASAC identified several concepts that need further clarification and consistent usage throughout the document. The first, of particular importance, is a clear explication and application of the "framework for causal determination." Second, definitions and characterization of "vulnerable" and "susceptible" need to be explicit, clear, and uniformly applied. Third, the role of exposure assessment, particularly in regard to the REA, needs better description. Continuing refinement of these concepts and their application in a consistent way will greatly improve the effectiveness and transparency of the ISAs.

The preamble would be even more effective if it included one or more, clearly annotated flow diagrams depicting the following:

- The ISA process;
- The various steps by which scientific evidence is considered and utilized, moving from the ISA to the Risk and Exposure Assessment (REA) and then to the Policy Assessment (PA); and
- The framework for causal determination.

Preface

The CASAC appreciates the addition of the Preface and agrees with the decision to include historical aspects of ozone regulation in the Preface. It is very helpful to have a timeline of the ozone standard regulation activities in one place. Perhaps a more appropriate name for the title of this section is "Historical Perspective." The CASAC applauds the inclusion of a complete reference list, particularly the previous ozone-related documents produced by the EPA. It would be useful if all the non-copyrighted documents were made publicly available, as is the case for all of the EPA publications.

Although the history of the NAAQS for ozone is useful, the CASAC notes several omissions, such as the discrepancy between the range of levels recommended by EPA staff (and the CASAC) and the final standard selected by the Administrator. Another omission is a description of the ozone standard reconsideration and the eventual withdrawal of the reconsideration in 2011. The CASAC suggests that the chronology should be expanded to address these events.

Chapter 1 (Executive Summary)

The CASAC finds that Chapters 1 and 2 comprise a useful and effective approach for presenting the summary information and conclusions. The Executive Summary is informative, accurate, and of an appropriate length. However, the Executive Summary could more clearly and less technically convey the key points of the ISA for the benefit of the public so that lay people, legislators, and others can easily identify the important conclusions of the document. An Executive Summary should convey the basic purpose, relevant context, methods, results, and conclusions, and this organization should be taken into account when revising this section. The CASAC suggests that it is appropriate for parts of this executive summary to overlap with major chapters of the overall ISA.

The CASAC is concerned about how the Executive Summary references material contained in the rest of the document. On the one hand, the current Executive Summary is easy to read and uncluttered because it lacks citations. On the other hand, it is difficult for a reader of the Executive Summary to find the location of expanded discussions of the topics in the rest of the document. One suggestion is to link the major rubrics with other chapters and components of these chapters as done in Chapter 2.
There are concerns with the integrative and/or conceptual figures. For example, the figure showing the transport of ozone in the stratosphere and troposphere is meaningful to a technical expert, but probably would be unclear to a lay reader. Similarly, there are concerns about the triangle/pyramid figure. The progression from items listed at the bottom to topics in subsequent layers is not apparent. These figures should be revised so that they are both accurate and clear to all readers. The chapter could also use thorough editing. Much of the text is awkwardly written (and/or punctuated), wordy, and unclear.

Chapter 2 (Integrative Overview)

The chapter on integrative health and welfare effects (Chapter 2) provides a useful and concise overview and the CASAC agrees with its position in the document. However, greater integration – as implied in the title – would be very useful. Although it includes most major topics, the pieces are not always assembled into a coherent picture. This chapter misses an opportunity for true integration: across the whole of the ISA, across disciplinary lines, and across various tools (modeling, scaling models up and/or down, the integration and use of models and field studies/empirical data). It would be very useful to add an overarching section that is truly integrative.

The CASAC recommends including more conceptual figures or flow diagrams to illustrate integration among components of the assessment. As with the Executive Summary, Chapter 2 should convey the basic purpose, relevant context, methods, results, and conclusions. However, Chapter 2 differs from the Executive Summary in that it is appropriately more detailed and technical. Chapter 2 should provide a clear idea of whether new findings confirm or change the conclusions of the prior assessment and what are the overall key findings, independent of date, that provide a foundation for the REA and PA.

The CASAC appreciates the attempt to include both conclusions from the 2006 ozone ISA and conclusions from the current ISA in Table 2-1 (p. 2-18). However, some conclusions from the current ISA are uninformative (e.g., "suggestive of a causal relationship") and some are not correct (e.g., the point on respiratory symptoms with newer findings from multi-city studies, potentially weaken earlier conclusions). Furthermore, causality determinations are not offered for many of the outcomes. Considering that the category "inadequate to infer a causal relationship" is one of the possible findings, causality determinations should be applied consistently throughout the table. In the current form, these tables are confusing and need attention.

Chapter 3 - Atmospheric Chemistry and Ambient Concentrations

Pertaining to estimates of background 0_3 concentrations, Sections 3.4 and 3.9 were updated and expanded to more fully describe the scientific issues associated with estimating background concentrations as well as the limitations and uncertainties of the methods used to estimate them. Section 3.6 on ambient 0_3 concentrations was revised to improve the description of variability in 0_3 concentrations attributed to diurnal and seasonal patterns, and spatial differences in urban and non-urban locations.

Please comment on the adequacy of these and other changes to the chapter and recommend any revisions to improve the discussion of key information. In relation to ambient and background 0_3 concentrations, is material clearly, succinctly, and accurately provided? Where appropriate, please provide guidance that may refine the scientific interpretation and/or improve the representation of the science.

This chapter, in general, provides a good overview of the atmospheric chemistry relevant to ozone pollution, the ability of models to describe it, and the ozone concentration patterns over the United States with particular attention to the background. The CASAC has been informed that supplemental section 3.9 on background ozone will be deleted; the CASAC strongly agrees with this decision.

Key areas of concern are summarized below. The first is the most important in the CASAC's opinion.

- The chapter needs to improve its connection to the eventual use of its findings in the REA and the PA. It should better discuss how the chosen areas of emphasis were guided by the needs of these documents, how the information will be used in these documents, and the level of confidence in this information. In particular, the presentation of background ozone needs a better synthesis of current knowledge and quantitative assessment of the related uncertainties.

- The discussion of background ozone, while solid, has some weaknesses that need to be addressed. Three new studies on background ozone (McDonald-Buller et al., 2011; Emery et al., 2012; Lin et al., 2012) should be discussed as they offer a much-needed resource for estimating uncertainties in the background ozone concentrations computed with GEOS-Chem. More focus needs to be placed on background estimates relevant to the annual fourth-highest maximum daily 8-hour average (MDA8) ozone concentrations. The discussion in the ISA needs to acknowledge the limitations of models in capturing the high extremes of the ozone distribution at remote sites, since these are often related to background ozone at least in the mountain west. For a given remote site, existing models may predict the mean ozone concentration well but tend to underpredict the high extremes of the ozone concentration distribution. It would be useful to draw a clear distinction between the mountain west, where elevated background may be a factor for achievability of a revised NAAQS, and the rest of the country, where it is not.

- Long-term trends in ozone over the United States warrant more attention than is presently given. These trends are important for accountability of emission controls, background influences, and effects of climate change. In addition to the EPA reports and the paper by Cooper et al. (2010) used in the ISA, there is an extensive literature on the topic including Parrish et al. (2009), Pegues et al. (2011), Leibensperger et al. (2008), and Lefohn et al.(2008). Trends have been very non-uniform across the United States, as acknowledged in the text. Maps should be added to better describe the heterogeneity of the trend data. Additional consideration of differences in trends for different quantiles of the ozone distribution, and different ozone averaging times (8-hour vs. 1-hour) would be very useful. Trends in the frequency of exceedances of 60-70 ppb thresholds would be particularly topical. The rollback model will require a number of model coefficients that are informed by the analysis of the temporal trends and how the distributions are responding to controls. A brief description of the rollback methodology would be useful, especially in regard to how it would reasonably preserve the background ozone concentration distributions.

- More discussion of the western oil/gas field winter ozone scenario may be helpful. There now are two known areas with high winter ozone: the Wyoming Green River Basin as noted, and the Uinta Valley (including Ouray) in Utah.

- Some more discussion of the value of satellite observations for ozone and its precursors would be appropriate. The limited discussion of satellite observations is inadequate and unenthusiastic. A more positive approach should be taken, given that satellite measurements have demonstrated usefulness for observing ozone in the free troposphere and for providing top-down constraints on NOx, carbon monoxide (CO), and volatile organic compound (VOC) emissions.

Chapter 4 - Exposure to Ambient Ozone

Revisions made to Chapter 4 in response to CASAC comments include clarifying the discussion of the relevance of central-site monitoring data for epidemiologic studies, together with potential bias and uncertainty due to exposure error; revising the summary section to be more concise and focused on the main points of the chapter; and preparing tables to summarize field study data and facilitate comparison of exposure models. In addition, material has been added discussing averting behavior on high-0_3 concentration days.

Please comment on the adequacy of these and other changes in responding to the Panel's comments. Please provide comment on revisions that may further improve the utility of discussion for characterizing personal-ambient exposure relationships and for interpretation of epidemiologic results in subsequent chapters.

The second external review draft of Chapter 4 is a significant improvement over the first draft, not only in terms of content, but also in terms of organization and scientific accuracy. The addition of tables that summarize the results of relevant studies is welcomed, as is the addition of new information and references. The chapter also does a good job of discussing what research is new since the last review.

Several additional changes to the chapter are recommended. First, the chapter should be revised to include a discussion of long-term ozone exposures, including how they relate to corresponding long-term ambient ozone concentrations and to potential confounding by co-pollutants. Since long-term personal ozone data are lacking, re-analysis of existing short-term ozone data or use of modeled exposures may be needed. Second, Section 4.5.3, which discusses results from personal exposure simulations at several different NAAQS level scenarios, should be reconsidered or deleted, as findings of geographic variability in the 8-hour ozone exposures of children estimated in the roll-back process are not supported by the data. Furthermore, the section is out-of-place in the ISA and may be better suited for the REA. Third, the analysis of population proximity to ozone monitors should be tied to maps of ozone concentrations, where ozone concentration and population data are presented together in the same analysis of monitor proximity. In the absence of data, modeling results shown in Chapter 3 could be used to explore whether population exposures and exposure error vary with proximity to monitors. Finally, findings from exposure studies should be integrated with discussions in Chapters 2, 5, 6, 7, and 8, as topics related to exposure error, confounding and highly exposed populations are important considerations for these chapters.

Chapter 5 - Dosimetry and Mode of Action

Chapter 5 was reorganized and updated in response to CASAC comments, including clarification of the linkage between dosimetry and mode of action, expanded discussion of species homology and key principles of 0_3 uptake, increased emphasis on underlying mechanisms which link to effects discussed in Chapters 6 and 7, and expansion of summary sections.

Please comment on the extent to which these revisions help Chapter 5 provide the underlying mechanistic and dosimetric information for interpretation of effects evidence in later chapters and recommend any revisions to improve the discussion of key information.

There have been numerous improvements in the organization and content of this chapter. The new overall chapter introduction clearly lays out the goals of the chapter. The background information on respiratory tract anatomy included in this introduction is also a useful addition. The elimination of the sectional subdivisions between research in the previous ISA and newer research has improved the flow and readability of the text. Furthermore, the mode of action (MOA) section has been refocused well. Although the revisions respond to the technical suggestions made by the CASAC during the previous ISA review, further improvement is needed in some areas, as summarized below.

Although dosimetry principles have been better explained in this second draft of the ISA, further clarification is needed. Early in the chapter, there should be a listing and definitions of the various dose metrics; these definitions should be used consistently throughout the chapter. In addition, the connection between dosimetry principles and theoretical or experimental observations of dose distribution and tissue damage should be discussed with more clarity and in more detail.

Within the section on Species Homology and Interspecies Sensitivity, the discussion of animal-to-human extrapolation modeling should be strengthened considerably due to its importance in the interpretation of toxicology studies cited in Chapters 6 and 7. This would include an introductory discussion indicating that there is solid evidence for qualitative extrapolation, such that if an ozone-induced effect is observed in an animal study, it is likely that such an effect could occur in humans if exposure were sufficient. Quantitative extrapolation (i.e., knowledge of equivalent effective exposures) is currently substantially more uncertain. The discussion should also stress that the relative ozone responsiveness among species is best judged by a properly normalized dose metric rather than by exposure concentration.

There also is the question of whether ozone alone or toxic products of ozone reactions with endogenous substrates is responsible for adverse responses. This is an important issue since the nature of a toxic agent affects its distribution among different respiratory tract regions, and this in turn determines the distribution of tissue damage. Chapter 5 emphasizes the importance of reaction products much more than the possible role of ozone alone. This point of view relies heavily on theoretical computations suggesting that ozone reaction in the epithelial lining fluid is so fast that unreacted ozone cannot penetrate to epithelial cells. A brief description of these computations and a discussion of the underlying assumptions should be added to the chapter. To this point, some literature indicates that the liquid lining layer is so thin in some parts of the respiratory tract that ozone might indeed reach underlying tissues.

It is well established that exercise plays a key role in human sensitivity to ozone. This revision of Chapter 5 has an improved description of breathing patterns during exercise and their effects on dose distribution. This material could be better linked to dose-response considerations in Chapters 6 and 7 by defining specific activity levels (e.g., rest, light, moderate and heavy) in terms of relevant respiratory conditions (e.g., minute volume per body surface).

The revised chapter provides a good foundation for understanding the relationships between exposure, dose, and effects observed in toxicology and human health studies. The authors should strive to improve the integration between this chapter and Chapters 4, 6 and 7, as well as the integration of the four sections within Chapter 5 itself.

Chapters 6 -7 - Integrated Health Effects of Short- and Long-Term Ozone Exposure

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. Tables, figures, and text were revised and/or created to provide additional details related to design and results of studies. In Chapter 7, the discussion of long-term exposure and mortality has been expanded with the addition of new study findings that provide additional evidence for this association.

Please comment on the extent to which there is sufficient clarity in the presentation of study designs and results. Please provide guidance where the interpretation of the scientific evidence may be improved as well as on the soundness of conclusions in these chapters.

This chapter has been substantially improved since the last draft. The chapter is better organized and figure legends have been clarified. The expanded text describing the studies is an improvement. The CASAC notes several additional areas for improvement.

- The text on the older studies is now more explicitly developed and integrated with the results from newer investigations and a smoother presentation of the materials is provided. Still, the focus on new scientific evidence should not be at the expense of summarizing the overall scientific evidence. The NAAQS is based on the full body of scientific evidence, not just the recent evidence. Key studies that existed during the last review should still be discussed. Although the intention to make the ISA more concise is appreciated, the document should clarify whether studies conducted since the previous review make a critical advance in the strength of evidence and their findings should be presented in the context of the previous studies. Not all previous studies need to be discussed, but key studies that still provide a basis of the overall scientific evidence should be incorporated. Tables may be useful to help summarize studies in a relatively concise manner. Rather than using a range of potentially vague terms (e.g., "new" and "recent") EPA could explicitly state that the ISA focuses on studies since the last review and use consistent terminology to distinguish these studies throughout.

- The acute and chronic animal toxicology studies and their implications to human health risk are not adequately described. As discussed in previous criteria documents, the toxicology data base is sufficiently strong to raise concerns about the range of effects that may occur in humans if exposures are sufficient. Adding key information on structural changes is especially important because they are observed at environmentally relevant levels in non-human primates and cannot be studied in humans.

- The EPA should consider changing the causal determination for the cardiovascular effects of short-term exposure to ozone (Table 6-53, p. 6-233) to "Likely to be a causal relationship". In CASAC's opinion, the evidence from toxicological, human clinical and epidemiological studies supports upgrading the classification for cardiovascular effects to the "likely to be causal" category. Moreover, this would be consistent with the determination of "likely to be a causal relationship" for cardiovascular-related mortality.

- The distinction between long-term and short-term exposure is still unclear, as Chapter 7 (long-term) has many studies that appear to be directed at acute exposure scenarios. This version of the ISA provides a definition of "long-term exposure" at the start of Chapter 7, which is a useful change from the previous version; however, the inclusion of short-term studies in the long-term chapter brings that definition into question. Exposures as short as a single day are not "long-term" exposures. These studies should be moved to the short-term exposure section. Although this will split the studies on birth outcomes, the format would then be consistent with how other health outcomes are treated in the document.

- The use of standardized exposure increments is an improvement over the previous ISA as results from different studies are more easily compared. However, the words "standardized increment" should not be used in place of a numerical value. The ratio among the daily 24-hour average, daily 8-hour maximum, and daily 1-hour maximum should be consistent throughout the ISA. In the current version, multiple ratios have been applied.

- The claim that "there is no apparent biological mechanism to explain the association observed for short-term O_3 exposure with cardiovascular mortality (p. 6-183, line 21)" is problematic. There are several potential mechanisms, such as pulmonary inflammation causing systemic inflammation, or triggering of airway receptors mediating autonomic effects, that could potentially underlie both short-term and long-term exposure effects on cardiovascular disease.

- Additional descriptions of the human clinical studies and their implications are warranted. In particular, the ISA should provide: (1) a clearer explanation of the lowest effective exposures in human clinical studies; (2) a description of the health impacts/severity of the key observed effects (especially spirometric changes, inflammatory changes, and symptoms); and (3) a description of the relationship of human clinical study protocols (including study participants, exposures, and activity patterns) to the "real-world" situation.

- One instance where newer study findings potentially weaken conclusions that were drawn in the 2006 AQCD is, somewhat surprisingly, that relating to respiratory symptoms and medication use in asthmatic children. Newer multi-city studies of symptoms in asthmatic children, which should arguably carry the most weight, are not convincing or show no association. The conclusions regarding respiratory symptoms and medication use in asthmatic children can therefore be questioned. The CASAC can assist in providing its assessment of these studies.

Chapter 8 - Populations Potentially at Increased Risk for Ozone-Related Health Effects

The introduction to Chapter 8 has been revised with expanded discussion to better capture the intricacies associated with characterizing populations potentially at greater risk for 03-related health effects, utilizing the terms identified by the CASAC panel (i.e. intrinsic, extrinsic, increased dose, greater exposure).

Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

Chapter 8 has been revised to incorporate language suggested by the CASAC as part of the prior review to better define the various terms used. The chapter has moved in the right direction as a result of these revisions. Some additional revisions would help further strengthen this chapter. The CASAC encourages the Agency to develop standard terminology and concepts for populations at risk that can be broadly applied across NAAQS pollutants.

Conceptual and definitional issues

This chapter needs to clearly distinguish two broad processes that can place populations at "increased risk":

- Greater ambient exposure and/or greater internal dose. People in this group include:

    - persons exposed to higher levels of ambient concentrations [for example, because of where they live, patterns of air conditioning use, or because of the activities they engage in (e.g., spend more time outdoors)]

    - persons who receive a greater dose at a given ambient level as a result of breathing pattern (e.g., the impact of exercise) or respiratory tract anatomy, and physiology. Factors such as lack of air conditioning also can enhance the internal dose received at a given ambient level. [Note that factors like breathing pattern can manifest themselves as effect modifiers in epidemiologic studies of ambient exposure (e.g., breathing pattern may modify the impact of ambient levels on disease risk), although this effect modification does not represent true synergism as it is simply due to differences in internal dose.]

- Greater adverse health effects given a specific dose.

    These are persons who have other characteristics that make it more likely that they will experience adverse health effects at a given dose. These "effect modifiers" may be biological (such as genetic variations or the presence of a pre-existing disease), behavioral (e.g., nutrition) or consequent to socioeconomic status (such as differences in access to care that result in greater emergency department visits or mortality when exposed to a given level of ozone).

The term "populations-at risk" as defined in the preamble and used in Chapter 8 appears to encompass both processes but this distinction could be clearer and further developed. If the terms "sensitive, vulnerable, or susceptible" populations are used anywhere in the document, they need to be clearly defined. For example, there should be clarity as to whether the term "sensitive populations" (which is employed frequently throughout the document) is used as a synonym for "populations at risk" (as defined by the two processes above) or whether it refers only to populations with greater adverse health effects at a given dose. The distinction between both processes should also be carried through in the review of the evidence.

Review of the evidence

Many diverse studies are reviewed, but often the evidence is not adequately summarized and interpreted. Additional synthesis highlighting the key conclusions that can be drawn from the studies would be helpful. The discussion in each section may need to reference biological mechanisms for interactions

discussed elsewhere (e.g., in Chapter 5). It also may link to effect modification discussed in other chapters (e.g., the chapters concerned with short- and long-term effects). It would be advantageous to develop simple categorizations that can be used to summarize and characterize the strength of evidence for magnification of adverse health effects by certain factors (or "effect modification"). For example, consider using categories like strong evidence of effect modification, suggestive evidence, little or no evidence, and limited data, paralleling the categories used for causation.

Discussion of methodological challenges

In the conclusion section, it would also be helpful to acknowledge some of the methodological challenges inherent in studying modifiers of ozone effects. Key among these are consistency in the measures of the effect modifiers studied and having sufficient sample size in the various cross-classified categories. These issues may explain some of the inconsistencies observed across studies. The EPA should consider integrating the section on "healthy responders" within this concluding section that highlights difficulties in investigating effect modification and notes that there is additional inter-individual variability in responses that are not currently explained by known factors, but need further evaluation.

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

The discussion of effects in Chapter 9 has been reorganized and consolidated into fewer, but more integrated sections to lessen repetition and improve the clarity of presentation. More discussion of ecosystem modeling approaches and more consideration of ozone impacts on stomatal conductance and water cycling have been added to the chapter.

Please comment on the reorganization and content of this chapter and the adequacy, scientific soundness, and usefulness of the material presented. Please recommend any revisions to improve the discussion of key information.

The EPA has captured well and responded appropriately to the issues of concern identified by the panel after the last ISA review. The chapter provides a sound summary of the current state of knowledge of ozone effects at scales ranging from the leaf to the ecosystem. The chapter incorporates new information (since the last AQCD) on the molecular and genetic underpinnings of ozone impacts, on available comparisons of chamber-based and more recently published chamber-less exposure studies, and the results of several meta-analyses that provide an integration of the previously available information. It also adequately summarizes the results of a series of ecosystem models that examine the effects of ozone on aspects of productivity. A table of causal determination should be included (such as Table 2-2).

Although no major changes to the chapter are necessary, a few specific areas do need attention. These include the reference to "sensing of ozone" by plants, which does not describe the process as currently understood; the lack of clear, unambiguous statements regarding the impact of ozone on root growth; and the lack of emphasis on ambient ozone effects on native vegetation. Further, the effect of ozone on water loss by plants (specifically, the potential for a decrease as well as potential increase in water loss due to sluggish stomata) should be incorporated into the discussion and overarching figures.

This chapter adequately integrates "old" and "new" research. In fact, the comparison of yield predictions based on exposure-response relationships using both open-top chamber and free air studies was compelling in its convergence, and a useful demonstration that "chamber effects" may be minimal in terms of assessing relative ozone impacts on plant growth and economic yield.

As with other sections of the ISA, some technical editing is necessary (see individual comments). In addition, there is still a lack of specificity and clarity about how, when and where "scale" is used. For example, the trees in the Aspen Free-Air Carbon Dioxide Enrichment (FACE) site are referred to as a "forest in Wisconsin" when in fact this is a young planted forest, and "ecosystem scale" is used to denote "bigger."

The addition of definitions and explanations of terms (e.g., hydraulic conductance, gross primary production, ecosystem respiration, net ecosystem production, net ecosystem exchange, photosynthesis and their relationships) would round out this chapter and make it more easily understood.

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

This chapter was made more concise, in part, by consolidating background material pertinent to both climate change and solar radiation into Section 1 0.1 . Section 1 0.2 was expanded and refined to clearly reflect the processes by which ozone contributes to climate change and the competing influences of ozone precursors on climate.

Please comment on the reorganization of this chapter and the adequacy, scientific soundness, and usefulness of the material presented and recommend any revisions to improve the discussion of key information.

Discussion of ozone as a climate-relevant gas is important in view of the need for concerted climate-air quality regulatory objectives in the future. Consideration of ultraviolet B (UV-B) effects is also appropriate although these appear to be very small. The chapter acceptably delivers on these two topics. A few areas of concern are summarized below.

- The discussion of projections for future global emissions of ozone precursors is based on the Special Report on Emissions Scenarios (SRES) of the Intergovernmental Panel on Climate Change (IPCC) Third Assessment Report (TAR) (2001), but these have now been superseded by the IPCC Fifth Assessment Report (AR5) Representative Concentration Pathways (RCP) scenarios. Even though there is a need to discuss the SRES scenarios since they have been used in most studies reported so far, the ISA should inform readers on the new RCP scenarios as these will be used in future literature. The RCP scenarios are radically different from SRES in trends of air quality gases and in particular, they do not project global increases in the future except for the business-as-usual scenario.

- The discussion of radiative forcing from ozone precursor emissions is inadequate. The IPCC bar chart on radiative forcing referenced to emissions would be a very important addition to this report. It would greatly help in educating the reader on the very different climate impacts of the different ozone precursors. Section 10.3.3 discusses older individual studies and becomes mired into details (such as the effect of aircraft NOx) but fails to convey the consensus generated in the IPCC AR4 report on the forcings by ozone precursor emissions. The numbers in the report

should be given here. In particular, an important conclusion of IPCC Fourth Assessment Report (AR4) is that NOx emissions are climate-neutral within the range of uncertainty.

- The discussion of UV-B effects is too long relative to the importance of the effect. It rambles and needs to more quickly arrive at the point. Calculating UV-B effects from changes in tropospheric ozone is a simple radiative transfer calculation. The effect is very small in model calculations (Madronich et al., 2011), and undetectable in observations, as would be expected. It seems that the chapter could easily be more conclusive in stating that the effect of expected tropospheric ozone changes on UV-B radiation is negligibly small and also provide a quantitative upper limit on the effect.

- Similar to prior chapters, bolded statements of causal determinations should be made in the chapter, and the text supporting those determinations needs to be consistent. Similarly, a table of causal determinations should be provided.

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Appendix A

Compendium of Individual Comments by CASAC Ozone Review Panel Members on EPA's Integrated Science Assessment for Ozone and Related Photochemical Oxidants (Second External Review Draft – September 2011)

Mr. George Allen

General comments:

The inclusion of the integrated summary (Section 2) is very useful; it makes the bigger picture much more accessible. These comments focus on Chapter 3. Overall this chapter is substantially improved over the March 2011 first draft.

More discussion of the western oil/gas field winter ozone scenario may be helpful in two ways. We now have 2 known areas with high winter ozone: the WY Green River Basin as noted, and the Uinta Valley (including Ouray) in UT (little to nothing is in the literature yet for this location). Understanding the relatively few and easily characterized precursor sources may add to our knowledge of many aspects of ozone formation, especially the roles of temperature and moisture. These locations may be studies of opportunity. Similar areas likely exist that do not currently have any monitoring. This may be worth noting in section 3.5, monitoring networks. Another area of new concern is the massive increase in fracking activities in many parts of the country; fugitive emissions and emissions from on and off-road HDD engines are a potentially new and large source of ozone precursors.

My previous comments referenced the 2011 Canadian Smog Science Assessment report from Environment Canada and Health Canada, an externally peer reviewed but not journal published document. It was scheduled to be released Dec. 2011. To the extent that Chapters 3 and 7 may be relevant to chapter 3 of the ISA, it would be worth a review.

Pg 3-1 line 15. Typo; reference here to Section 3.1 should be 3.5.

Pg 3-5 lines 29-30, and elsewhere re: on-road NOx emissions. With rapid changes to HDD NOx controls coming into effect, the inventories may lag or become more rapidly outdated. To the extent that this may be relevant to this discussion, it could be noted. It is an on-road analog to the NOx SIP call in 2003.

Pg 3-10 line 10. CNG vehicles can be a large source of formaldehyde; if this fleet continues to expand in urban areas without proper emission controls, it may become a larger factor in urban inventories.

Pg 3-14 lines 21-27. Long et al. (J. Air & Waste Manage. Assoc. 50:1236-1250) may be another source for quantitative understanding of SOA generation from ozone and pinenes.

Pg 3-16 lines 23-35. See general comments above regarding high winter ozone in rural industrial valleys.

Pg 3-18 lines 6-22. Good quality routine (non-research) NOz measurements remain scarce. EPA's intent to develop a NOy reference method for possible future NOx-SOx NAAQS may also benefit the understanding of the relationship between NOz and ozone.

Pg 3-20 and elsewhere re: NOx emission trends in the eastern US. Similar to expected decreases in on-road NOx (Pg 3-5 above), stationary source NOx emissions may be further reduced by the "transport" rules (CAIR, CSAPR, etc.). Together these control programs may reduce NOx emissions relatively rapidly and thus potentially change the landscape of high and low NOx regimes. Another factor that

could push more areas into low NOx regimes is that additional substantial reductions in anthropogenic VOCs will not come readily or cheaply due to the distributed nature of the sources.

Pg 3-28 lines 29-35, extending the CMAQ domain in the northern hemisphere

Pg 3-29 lines 5-11. Sentence structure problem.

Pg 3-31 lines 26-32 and elsewhere. From a NAAQS perspective, the examples of remote NA background O3 may be more useful if expressed in the current NAAQS form (98^{th} %tile, 3-year mean).

Pg 3-34 lines 28-37. There will be much more coming out of the long Mt. Washington NH summit high elevation data record, but perhaps not in time for inclusion in this round of the NAAQS review. The year-round ozone measurements started by UNH/AIRMAP have been taken over by the NH Dept. of Conservation air monitoring program; those data are in AQS, and a year of collocated data were collected during the transition. This extends the data (starting in 2001) from the end of AIRMAP monitoring in spring 2010 (not in AQS) through the present and presumably the foreseeable future. These data are helpful in characterizing stratospheric intrusion as well as long term trends in long-range transport in the northeast US. Yaping Xiao (UNH/AER) has work in progress on this analysis.

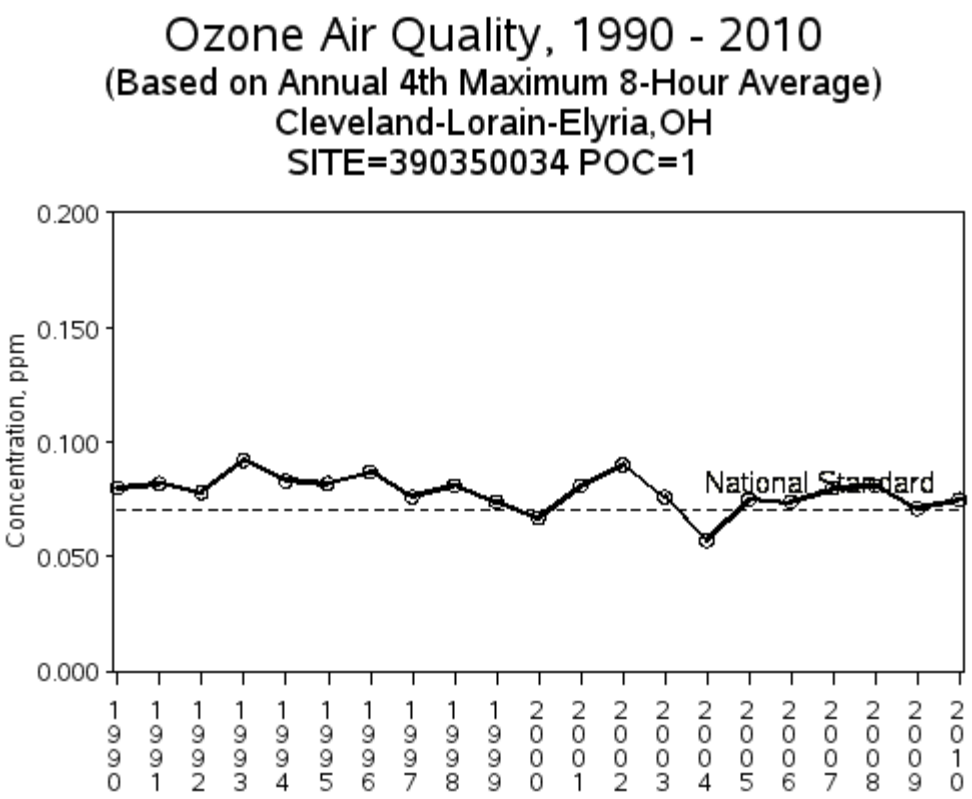
Pg 3-46 to 3-49, section 5.3.1 (monitoring methods). There has been much discussion over the last decade of interference issues from FEM UV monitors. This section summarizes the work well. Taken as a whole, concerns about positive interferences in the UV monitoring method do not seem to be relevant in the context of compliance monitoring. The cases of substantial interferences are limited and unlikely to have a meaningful impact on ozone design values. Overall, the quality of contemporary ozone data (3.5.2 through 3.5.4) are very good relative to data quality for other NAAQS pollutants.

Pg 3-55, section 3.5.5.2. NO-based chemiluminescence ozone monitors appear to be a robust measurement technique and are now commercially available. The TAPI instrument is a good candidate for a revised ozone FRM in this round of the review.

Pg 3-70-71 and elsewhere. The number of year-round ozone site has increased substantially since 2009, with the 2011 implementation of NCore monitoring and other initiatives. It may be worth noting for reference the number of ozone monitors reporting for the winter of 2011-2012.

Pg 3-95 lines 10-17. I strongly agree with the caution about approximating community-scale exposures from the relatively sparse (relative to expected spatial variability) urban monitoring network.

Pg 3-103-105, multi-year trends. These trends are very important in assessing progress in ozone control programs. Pg 304 line 13-14 notes that Cleveland is among the cities with the largest reductions in ozone from 2001 to 2008. However a 20-year (1990-2007) ozone trend from a Cleveland monitoring site (39-035-0034) shows no meaningful change.



Source: EPA trends report, http://www.epa.gov/airtrends/ozone.html#ozloc

Pg 3-112, section 3.7. This Chapter Summary section is very useful in pulling together the information presented in the previous 111 pages. It complements the integrated summary (Chapter 2) nicely.

Sections 3-8 to 3-10 (supplementary material). Moving this material to this section substantially improves the readability of section 3 while keeping the details behind the other sections readily available.

7.2.7, pg 7-28 lines 10-11 and elsewhere in section 7. Reference to Zanobetti and Schwartz [O3 susceptable chronic mortality] needs updating; the article is no longer in press.

Dr. John Bailar

I regret that I was not able to attend the meeting. However, I have read relevant parts of the draft report, and two issues trouble me. Both have implications for EPA that extend beyond the ozone report.

First is that the report should include a statement that the strength of evidence for an effect on a broad category of outcomes cannot be lower than the strength of evidence for some component. For example, one cannot have an increase in cancer of the lung without an increase in total cancer (whether there is direct evidence of that or not) except in the unlikely event that there are compensating decreases elsewhere. I have seen no evidence for any such protective effects of ozone in this context. EPA's position and reasoning on this might be covered in a single paragraph is if it sufficiently clear, pointed, and prominent.

However, a better solution would be to simply delete any summary statement about over-broad categories, such as all cancers combined. This would make biological and medical sense as well.

Second is the need to note in the text, again in a prominent place, that the summaries are not intended to provide "best judgments". One would expect a consensus best judgment to come out in the middle of informed opinions, and to move up or down with roughly equal frequency. EPA's limits, for all sorts of things, do not do that. By my reckoning some years ago, and from my casual observations since then, about 90% of changes in mandatory or recommended limits to chemical exposures are downward, and many of the remaining 10% cannot be classified one way or the other (for example, a change from a STEL to lower TLV). This is strong evidence that the summary judgments and exposure limits are tailored to what can be most successfully defended rather than to improving the public health.

Dr. Michelle Bell

Comments on Chapter 6: Integrated Health Effects of Short-Term Ozone Exposure

EPA has greatly improved this chapter. It is clear that a substantial amount of thoughtful work has gone into the revision. The document is more clearly written and better organized. Attention has been given to many of the concerns raised by CASAC, such as the use of the consistent terminology and organization, the presentation of results, and clarity. Although the new version is quite a bit longer, I view the additional text as quite worthwhile. In particular, individual studies are better described. Needed detail has been added to the issue of confounding by co-pollutants. Tables and figures are better labeled.

A major improvement is the use of a standard increment of ozone to allow comparability among results in the tables and figures. I appreciate that these results are noted as "standardized" in the tables and figures. Although the standardization of ozone increments was necessary, it may be a bit confusing to some readers. There are two key ways to address this. First, the footnote describing the conversion (page 6-25) could be moved to the main text. Second, be careful about text such as "standardized increments" were associated with a specific health change. In order for such sentences to be meaningful, they have to state the actual ozone increment. There is nothing "standard" about EPA's chosen standardized increments (although they are appropriate), so I would shy away from such language like "3-8% per standardized increments in O3" (page 6-39) in favor of stating the specific ozone increment.

There are a few places where terminology is still a bit confusing. Many of these issues can be fixed by a careful review of the document, but may relate to a broader issue. As an example, there is no need to use "recent" or "new" when referring to a specific study (such as on page 6-10, 6-16, 6-34, 6-45, and many others). It's not clear what is meant by a "recent" study in this context, especially as many studies in the past year or two fall into the category described as less recent ("groups with increased outdoor exposures or other healthy populations"). This relates to a larger issue of the false distinction between studies that were incorporated into the previous ISA and newer studies. I suspect that "recent" is used throughout to alert readers to studies that are newer than those in the previous ISA. As discussed in our previous CASAC meetings, there is a bit of a false distinction as the NAAQS will be set on the weight of overall scientific evidence. However, we recognize the desire to have a (relatively) short document. There is no perfect solution here, but EPA needs to make a conscious decision on how to distinguish between older and newer studies, without resorting to vague terms like "recent" or "newer." It would be preferable to expand to "since the previous ISA" or something more specific.

Evidence for a specific type of cause is often based on studies using slightly different ICD codes (e.g., table 6-25). This could be mentioned explicitly in the text as a minor limitation.

There are a few typographical errors (e.g., "decrease lung function" should be "decreased lung function" page 6-53; title of Figure 6-15 runs into the section title on page 6-123).

The tables and figures often have different fonts and font sizes. In a few cases, the text is too small to read easily. The lack of a consistent format is a bit distracting.

Several studies have been published since this writing of the ISA. Are new, relevant studies to be added? Of course, at some point there has to be a cutoff for new publications to make the process more manageable.

Given the evidence of ozone and mortality, the determination of "likely to be causal" is a bit cautious.

Comments on Chapter 7: Integrated Health Effects of Long-Term Ozone Exposure

This chapter is has been benefited from the revisions. In particular, the phrase "long-term exposure" is more clearly defined at the start of the chapter and used consistently, with exposure timeframes defined throughout the text. This is a substantial improvement. It is still not perfectly clear what "chronic" means in this chapter.

The definition of "long-term" in this chapter is still a big confusing. The first paragraph defines long-term exposure as a duration of 30 days (1 month) or longer (page 7-1), and while it is very helpful to have this definition, there is a section on neonatal mortality for exposures less than 1 month (Section 7.4.10.3). Other studies mentioned in Chapter 7 refer to even shorter timeframes. For examples, see studies on infant mortality with exposure timeframes of 1-3 days. There is also mention of results for single day lags of L0 to L6 in Table 7-6. Table 7-10 has short-term studies for 10 days. This is problematic. Either remove short-term studies from Chapter 7, or change its title. If it is simply not possible to avoid short-term studies in this chapter, add a note to the start of Chapter 7 (perhaps after the definition of "long-term" to alert the reader that these studies are discussed in this chapter and why).

The tables and figures have been revised and are better labeled; however, there are still places that need clarification. Please review all the tables and figures to make sure they are clear. An example is Figure 7-3, which presents the ozone-asthma concentration-response relationship, but does not describe what is meant by "asthma" (new asthma, use of asthma medication, prevalence of asthma, physicians' visits). This figure needs a citation. It looks to be taken directly form a journal article, possibly from Environmental Health Perspectives. Table 7-3 provides "results" but does not say what these are (an OR for a given health increment). The column "exposure" in Table 7-3 refers to the exposure increment used for the results, not the overall exposure levels of the study. The value of "high O3 > 50 ppb" is unclear, and probably means risk at values above that level to risk at values below that level. The description of figures is inconsistent. Sometimes the description notes that error bars represent 95% intervals (e.g., Figure 7-4), whereas in most cases this is not included. Table 7-6 has a footnote that is not used well in the table. It states that the effect estimates are in units of a 10 ppb change, but portions of this column also have a different footnote saying a 1 ppb change is used (change footnote a to "unless otherwise specified").

The comments above (for Chapter 6) regarding the terms "new" and "recent" and the distinction between old and new studies also applies to this chapter, although overall this chapter suffers from that problem less than Chapter 6.

The issue of units of the increment for exposure in effect estimates is still a problem in this ISA. Chapter 6 has estimates converted to standard increments to aid comparison, with 40 ppb, 30 ppb, and 20 ppb for 1-h max, 8-h max, and 24-h average, respectively. Parts of Chapter 7 use different increments, which is not such a huge problem as the chapters differ in terms of short-term and long-term exposure, but there is no real benefit of using different increments. As an example, Table 7-6 uses a 10ppb change in ozone

for both the daily 24-hour average and the daily 8-hour maximum, and a 1 ppb change for the daily 1-hour max. It is not appropriate to have the same increment for the 24-hour average and the daily 8-hour maximum. Another set of results in Table 7-7 use still a different set of increments with a 10ppb for all three ozone metrics. The ratio of increments differs across chapters and within Chapter 7 (4:3:2 for the 1-h max : 8-h max : 24-h average in Chapter 6; 10:10:1 in Chapter 7; and 1:1:1 in Chapter 7). Further, the ratios used in Chapter 7 are themselves not appropriate.

Dr. Joseph D. Brain

Preface, Preamble, Chapters 1 (Executive Summary) and 2 (Integrative Overview)

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy of these summary sections and the conclusions therein.

The CASAC panel expresses appreciation for the major revisions that have been made in this revision of the ISA. Specifically, we applaud the new Preamble, which not only supports this particular ISA, but others as well. Greater uniformity among CASAC documents will be helpful to the agency and to the public. Further scrutiny and review of the Preamble is warranted, not because of substantial problems, but because of the potential future role of this document. I believe that the authors of the Preamble should be identified, and this Preamble should be submitted to an ATS journal or perhaps to Environmental Health Perspectives for peer review and publication. Or perhaps a free-standing Preamble can simply be adopted by the EPA and endorsed by CASAC. Its substance and its future use is too important for it to be overlooked as part of this larger and not widely circulated document.

There is an elephant in the room that CASAC and/or the EPA Ozone Panel should address. Ozone concerns make clear that we need to revisit the Clean Air Act. It is now more than forty years since the Clean Air Act was passed in 1970. It has had an enormous positive influence on health and even has contributed to the economy. However, is it still possible to established air quality standards "allowing an adequate margin of safety…to protect the public health"? We are increasingly aware of susceptible individuals and it is clear that current ozone levels at the current standard have measurable health effects. Is it possible and practical to make further reductions in the standard and in ambient levels?

This problem has become more serious now that the EPA has established a "policy relevant" background level, which appears to range from 0.015 to 0.05 ppm. The ozone standard is approaching background concentrations. I recommend that our committee and CASAC propose that we address this problem. While doing this, we need to be certain that we don't threaten the regulatory process and its historic successes. But if we don't address this challenge, this may also threaten the credibility of the Clean Air Act and the regulatory process and even the role of CASAC.
Of particular importance is clarifying the "framework for causal determination." Continuing clarification of this framework and using it in a consistent way has greatly improved the effectiveness and transparency of ISAs.

I very much appreciated the Preface. It's very helpful to have a historical review of the ozone standard and a discussion of what has happened in the last couple of years. I like having this "story" told in one place. Is Preface the right word? Should it be called "Historic Perspective" or something like that?

We agree with the conclusion in the charge question that Chapters 1 and 2 now "comprise a useful and effective approach for presenting the summary information and conclusions." The executive summary is now seventeen pages long. That's an appropriate length. Lay people, legislators, and others can conveniently read the key points of the document. I'm not concerned that several parts of this overlap

with other parts of the overall ISA. They should. The tables and figures add a lot. The summary is informative and accurate.

I do have one concern. If the reader wants additional information on any particular topic, such as 1.4 Human Exposure or 1.6.4 Populations at Increased Risk or whatever, do we need to guide them to sources and expanded versions of these topics? On the one hand, the current executive summary is easy to read and uncluttered because it lacks citations. On the other hand, how does a reader of the executive summary find an expanded version of the topics addressed here? Perhaps one way is to link the major rubrics with other chapters and components of these chapters. Then one could go there and use other aids, such as HERO to move to an expanded version of the summary as well as the references which support them.

Another solution is to make clear that the integrative summary – to some extent – is an expansion of the executive summary. In similar fashion, how do we move from the integrative summary to the other chapters which support it? It's possible to move from the executive summary to the integrative summary to the remainder of the document, but are there ways in which these paths can be better defined and easier to use?

A major concept of importance is "policy relevant background." I don't see that addressed in the executive summary. Similarly, in Chapter 2, the integrative summary, I also don't find discussion of it.

We applaud adding introductory sections which are specific to this ISA and placing them at the beginning of Chapter 2. We agree that it makes sense to include historical aspects of ozone regulation in the preface. In toto, this makes sense and presents a more logical progression and a more accessible document to readers at multiple levels.

I confess to remaining ambivalent about the length of the ISA. This latest revision is still very long. On the one hand, its length makes it difficult to find key ideas and to focus on what information is most relevant to a review of the current standard. On the other hand, there are so many aspects to understanding ozone toxicology as well as an abundance of new information that leaving things out also seems undesirable. These current revisions and especially the chapter on integrative health and welfare effects (Chapter 2) is a useful and concise overview.

Comments on Other Sections: 1. I draw attention to sections dealing with adaptation. One of the hallmarks of oxidant injury, especially ozone, is the phenomenon of adaptation. There are levels of ozone, or hyperoxia, which produce serious injury or even death in naïve animals. However, in animals chronically exposed to lower levels of ozone or oxygen, there is morphologic and biochemical adaptation. Subsequent exposures to ozone produce a far lower response. This is important in understanding ozone toxicology in humans as well. It also relates importantly to different patterns of ozone exposure. Citizens, who rarely see significant ozone levels and then suddenly have a two to three day episode of high ozone, may be much more affected than those who enjoy steady state ozone exposures all the time.

<u>Minor Comments</u>:

Preamble, Page lv. I'm not sure I am convinced of the first sentence of the second paragraph, lines 15-16. Is it the case that "the most direct evidence of a causal relationship between pollutant exposures and

human health effects comes from human exposure studies"? The paragraph then goes on to describe the deficiencies of such studies. An important one not adequately discussed is the fact that the outcomes for such deliberate human exposures must, by definition, be trivial. More severe exacerbations, causing cardiopulmonary disease, aggravating it, or events leading to hospital admissions or mortality – all the things we care about deeply – cannot be addressed in controlled human exposures. It may be true that these studies loom large at the lowest levels of observed ozone effects, but our overall concern about ozone flows more strongly from more serious outcomes detectable by epidemiology and predicted by relevant animal studies.

Dr. David Chock

Comments on the Preface, Preamble, Chapters 1 and 2

This portion of the revised version has greatly enhanced the value of the ISA to its readers. The organization is logical and the presentation is concise and thorough. The authors have done a wonderful job. I have nothing to add except for some minor editorial issues: In Chapter 1, references to tables in the text ought to be by number (e.g., Table 1-1) rather than by location. Presently, Table 1-1 is placed before the text that refers to it as "table below" (Section 1.6). Also, Chapter 1 has no page numbers and line numbers.

Comments on Chapter 3: Atmospheric Chemistry and Ambient Concentrations

This Chapter is very well prepared and represents an excellent summary of our scientific knowledge to date on tropospheric ozone. Section 3.4 points out that any existing monitored ozone concentrations are inadequate to represent North American background (NAB) because any anthropogenic emissions in NA can travel short and long distances to impact all monitors (See page 3-32, lines 16 to 20). Consequently, the NAB needs to be determined by chemistry-transport models (CTMs) such as GEOS-Chem. Section 3.9 is an excellent update of the GEOS-Chem model predictions for different definitions of ozone background. Yet there are issues of model performance that need to be more thoroughly described in the Sections, especially in regard to extreme concentrations relevant to the ozone air quality standard.

Section 3.4.3 discusses ozone background estimations. But there are limited discussions of the extreme value estimates of the ozone background distributions, especially the annual fourth highest values of the daily-maximum 8-hour ozone concentrations. This information is important in the process of setting the NAAQS for ozone when the intended standard is approaching the background concentrations. Figures 3-49 through 3-56 of Section 3.8 show many time series comparisons between measurements and GEOS-Chem model predictions of daily maximum 8-h ozone concentrations for many CASTNET sites in 2006. The comparison for the Trinidad Head site (See Figure 3-55) is particularly interesting because ozone concentrations at this site are quite close to the model-predicted North American background values. While the predicted and observed annual means of the daily-maximum 8-hour ozone concentrations appear quite comparable, it is rather obvious that GEOS-Chem underpredicts the upper extreme values of the concentrations. Assuming that the observed means can be relatively well predicted, it is generally true that chemistry-transport models have difficulties predicting the upper extreme ozone concentrations and, in fact, tend to underpredict them compared to actual observations. (It would be nice if figures similar to Figure 3-11 on page 3-36 of the first draft were included in the current draft.) These underpredictions make it difficult to use CTMs to construct a reliable NA background for regulatory purposes. Note that the distributions for the observed and GEOS-Chem-predicted daily maximum 8-hour ozone concentrations for the high-elevation CASTNET sites during March-August of 2006 (see Figure 3-58 of Section 3.9) look reasonable for the mean and the high end of the distributions. But these are combined distributions of multiple sites, which do not establish the accuracy of model predictions for individual sites. And the air quality standard is supposed to be met by each individual site.
Section 3.7.2 discusses the role of fine-scale modeling. An issue that has almost never been discussed is the role of subgrid chemistry. All existing CTMs assume uniform chemical reactions within a model grid. But when the time scales of some chemical reactions are short relative to the mixing time scale of

the constituents within the grid, spatially non-homogeneous chemistry will occur. Because the range of atmospheric chemical reaction time scales is large, ignoring subgrid chemistry most definitely contributes to modeling errors. Yet the error size is very difficult to ascertain because of the complexity of the nonlinear atmospheric chemical reactions. (Incidentally, contrary to the figure caption, the right panel of Figure 3-56 does not contain a comparison of GEOS-Chem model predictions of different grid resolutions.)

On page 3-3, lines 10 to 13, the description of the role of high-pressure systems in causing high ozone is somewhat confusing. Sinking air associated with a high-pressure system may not necessarily increase stability and decrease vertical mixing because the associated cloudless skies of the high-pressure system, while increasing stability at night, actually promote mixing within the planetary boundary layer in the day time. A more cogent argument, which is also implied in the subsequent description, would be that cloudless skies in the daytime promote photochemical reactions, and sinking air could bring down the high ozone concentrations trapped in the previous night in the lower free troposphere, due to low winds and deep penetrative convection during the day.

Comments on Chapter 4: Exposure to Ambient Ozone

The second external review draft of Chapter 4 is a significant improvement over the first draft, not only in terms of content, but also in terms of organization and scientific accuracy. Tables are now provided that summarize the results of many relevant studies. New information and associated references have been added. In particular, the inclusion of a discussion on averting behavior on high-ozone alert days is helpful. It shows a significant beneficial impact of alert information on asthma hospital admissions for children and the elderly. The Summary and Conclusions section has been shortened and it presents a more concise and accurate description of the Chapter.

There are two issues that the Chapter authors need to pay attention to. First, in Table 4-3 (p. 4-13), most of the results presented appear to be the slopes, rather than the "ratios" as indicated in the table title, for the relations between personal exposure and ambient concentration for a given time duration. We don't expect the ratio and the slope in a linear regression to be the same unless the intercept and terms like the random-subject effect in the regression model are effectively zero. And there is no indication in the text that this is the case. If the entry for Xue et al. (2005) in the table is any indication, the values for ratio and slope can indeed be quite different.

Second, in Subsection 4.5.3 describing microenvironment-based models, there is a paragraph describing the impact of roll-back adjustment on air quality distributions (p. 4-31, lines 13 to 22). It indicates a vastly different estimated probability of exposure to an 8-h ozone level of at least 70 ppb between children in Boston and children in Los Angeles, when both cities are assumed to meet an alternative 8-h ozone standard of 74 ppb. There is no indication as to whether this is a scientifically reasonable outcome when both cities indeed meet the said standard. In fact, it is most likely not. If the rollback adjustment used is the quadratic rollback for concentrations above the mean of the policy-relevant background (PRB), then obviously the true PRB distribution has been distorted as a result because the portion of the PRB distribution above the PRB mean has been suppressed, more so in the case of Los Angeles than Boston because of a more drastic reduction requirement. This is unphysical and is an artifact of the selected rollback methodology. The content of this paragraph is more speculative than definitive, and it only reduces the scientific credibility of the Chapter. Its removal is strongly recommended.

Two editorial errors are identified below:

Page 4-18, lines 7-8. The sentence is incomplete.

Page 4-22, line 22. “Figure 3-24” should now be changed to “Figure 3-25” in this version.

Dr. Ana Diez-Roux

Charge Question 8 - Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

Chapter 8 has been revised to incorporate language suggested by CASAC as part of the prior review in order to better define the various terms used. This has helped clarify some of the ambiguity present in the prior version. However, given the importance of the identification of "sensitive" groups for the NAAQS generally, additional clarifications (and accompanying tightening of the language) may be helpful. It is also important to be consistent throughout the ISA in how the various relevant terms are defined and used. Some reframing of how the material on "populations at increased risk" is presented may also be helpful.

Conceptually it is important to distinguish two broad categories:

1. Persons exposed to higher levels of ambient concentrations [for example, because of where they live or because of the activities they engage in (e.g. spend more time outdoors)].

2. Persons who are "more vulnerable" to the adverse health effects of exposure to a given ambient concentration. Persons who are "more vulnerable" are persons who have other characteristics that make it more likely that they will suffer adverse health effects when exposed to a given ambient concentration. In epidemiologic studies this differential vulnerability is manifested through the presence of statistical interaction between ambient levels and other factors or through the equivalent "effect modification" (when the adverse health effects of air pollution are different depending on whether another factor is or is not present). A simpler terminology for this category which avoids the use of the term "greater vulnerability" (which may lead to confusion given past uses) may be "persons with characteristics which magnify the adverse health effects of a given level of exposure."

This "greater vulnerability" (or magnification of the adverse health effects of a given level of exposure) can result from various processes:

(a) characteristics that modify the dose received by the individual for a given ambient concentration. This includes breathing patterns (which modify the internal dose) and air conditioning which modifies the indoor exposure. Note that if "exposure" is defined broadly to encompass the (internal) dose received by the person, both of these factors can be considered to be related to exposure levels (rather than to modifications of the effect of exposure) and could be encompassed under point 1 above. However, practically speaking what is commonly measured in studies is the ambient exposure, so both of these factors operate as effect modifiers in studies of ambient levels (ie the strength of the relation between ambient ozone and adverse health outcomes is modified by breathing patterns and/or by air conditioning because both affect the actual internal dose received).

(b) characteristics that interact synergistically (and ultimately biologically) with exposure such that the adverse health effects of the dose received are greater (or only present) when the characteristic is present. There may be many personal characteristics that interact with air pollution exposures, such that the adverse effects of air pollution are magnified. Some of these may be eminently biological (such as

genetic variations or the presence of a pre-existing disease) and others may be more social (such as differences in access to care that result in greater mortality when exposed to a given level of air pollution). Age or lifestage may also modify the adverse health effects of air pollution although at least part of the modifying effects of age may reflect differences in breathing patterns or presence of other diseases.

It is important to note that some population attributes such as low socioeconomic status or certain race/ethnic groups may both (1) be linked to exposure to greater ambient concentrations (through work or residential exposures) and (2) magnify the adverse health effects of exposure through interactions of various factors linked to SES and race/ethnicity with air pollution (e.g. greater prevalence of pre-existing conditions in lower SES groups, interactions of air pollution with other risk factors such as unhealthy diets, or poor access to care). Gender and other factors may also have implications for both sets of processes.

Although all the elements listed above are mentioned in Chapter 8 and throughout the ISA, the framework within which they are presented is not as clear as it could be.

"At-risk population" (which is used to encompass populations variously described as "susceptible, vulnerable, or sensitive") is defined in the preamble as "those populations or life stages that have a greater likelihood of experiencing health effects related to exposure to a pollutant due to a variety of factors. These factors may be intrinsic such as genetic or developmental factors, race, gender, life stage, or the presence of preexisting diseases or they may be extrinsic such as socioeconomic status, activity pattern and exercise level, reduced access to health care, low educational attainment, or increase pollutant exposures (such e.g. near roadways)" (pg xiv).

This is a broad definition that encompasses population features associated with either (1) greater exposure or (2) with factors that magnify the adverse health effects of exposure although this distinction is not made explicit. Chapter 8 restates a similar definition although some of the language in the introduction seems to suggest that the focus of the chapter is not on increased exposure but exclusively on increased vulnerability to a given level of exposure. Section 8.10 on "Heightened exposure" does include a discussion of increased exposure (primarily due to type of work and air conditioning availability) but it seems to be a bit of an afterthought and is not well integrated within the rest of the chapter or sufficiently comprehensive.

If the intent of Chapter 8 (and the term "populations-at-risk) is to allude to populations who have higher levels of exposure and/or who are more vulnerable to a given level of exposure it may be helpful to consider reframing the information presented so that (a) factors related to greater exposure and (b) factors that magnify the adverse health effects of exposure are clearly distinguished both in the introduction and in the discussion of specific studies.
It could be practical to being with factors related to greater exposure and then discuss factors that modify the adverse health effects of a given level of exposure.

The section on increased exposure could review work showing variations in levels of exposure by key sociodemographic attributes. Work on the modifying effects of breathing patterns or air conditioning could also be reviewed here, as the "effect modifying" effect of these factors is primarily a result of reductions in internal dose or exposure.

The section on factors that magnify the adverse health effects of exposure could be categorized from more proximal to more distal. For example successive categories of effect modifiers discussed could be (1) genetic factors (2) pre-existing disease/conditions (3) other disease risk factors (smoking, diet, BMI, physical conditioning); (4) sociodemographic factors including lifestage, gender, race/ethnicity, SES (which could modify the effects of ozone in part through the more proximal mechanisms).

These suggestions do not imply a radical revision of this chapter which has excellent material but rather a reorganization and reframing. The need to develop this type of general framework was also alluded to in the prior CASAC review.

In general, it would be helpful if each section on an effect modifier had a similar structure (this is done for some sections but is not always consistent): (1) rationale for expecting effect modification of ozone effects specifically with reference to hypothesized mechanisms (this is especially important for more distal factors such as SES and race/ethnicity which could modify ozone health effects through a number of different mechanisms) (2) prevalence of the condition or factor in the population as a way to highlight the population health importance of any effect modification observed (3) synthetic review of key epidemiologic studies clearly distinguishing studies that found effect modification and those that did not (rather than just listing all studies, large and small sequentially) (4) review of any controlled experiments or toxicological studies to highlight mechanisms and biologic plausibility of effect modification (5) general conclusion.

It would be helpful for the reader to get a sense from the literature review of how often this particular factor has been investigated as an effect modifier and whether the studies have been large or small. As is the review simply lists a number of studies with sometimes inconsistent results so it is difficult to get a clear sense of what can be concluded or whether much additional work is needed to clarify the importance of the specific effect modifier. Some statements on the criteria used to select the studies highlighted would be helpful.

In general there are several instances where the language can be sharpened. Often the description of effect modification is not precise (e.g. “factor X increases ozone risk” rather than “factor X magnifies the effect of ozone on risk of disease Y”).

In the conclusion section it may also be helpful to acknowledge some of the methodologic challenges inherent in studying modifiers of air pollution effects. Key among these are consistency in the measures of the effect modifiers studied and having sufficient sample size in the various cross-classified categories. These issues may explain some of the inconsistencies observed across studies.

Specific comments

pg. 8-2. The detailed discussion of intrinsic and extrinsic factors may not be necessary since as noted in the chapter, the distinction between both types can be rather arbitrary

pg 8-4 The conclusion of the section in influenza/infections does not appear to match the studies that are reported, most of which appear to report effect modification. The rationale for the conclusion that there is little evidence of effect modification needs to be further developed.

Pg 8-10. A brief summary of all of section 8.1 (linking all pre-existing conditions /diseases to differential ozone effects) would be helpful.

Pg 8-13 The conclusion of section 8.2.1 (Children) does not seem to match the bulk of the evidence presented. A clearer statement of what the evidence shows regarding whether children are or are not more vulnerable to the effects of ozone would be helpful.

Pg 8-14 to 8-16. Sections on older adults and gender. This is clearly a difficult literature to summarize with sometimes inconsistent findings. Sometimes the many studies reviewed are difficult to follow. Greater synthesis (for example first noting all studied reporting effect modification and the noting exceptions) might help give readers a better sense of the bulk of the evidence.

Pg 8-18 to 8-22 The section on genetics is much longer than the others and could be condensed.

Pg 8-30 Consider reframing section on "heightened exposure" along the lines suggested in the general comments so that a broad range of factors related to greater exposure are discussed. Factors that result in greater internal dose (such as breathing patterns) could also be mentioned in this section, although noting that this is manifested as effect modification in epidemiologic studies.

Pg 8-26 lines 20-23. The sentence is unclear. Was there effect modification by census tract household income? What does "regardless of SES" mean?

Pg 8-32 Consider integrating the section on "healthy responders" within a concluding section that highlights difficulties in investigating effect modification and notes that there is additional interindividual variability in responses which are not currently explained by known factors but need further evaluation.

Dr. William Michael Foster

Charge Question on Chapters 6 and 7: Comment on the extent to which there is sufficient clarity in the presentation of study designs and results; and provide guidance where the interpretation of the scientific evidence may be improved as well as on the soundness of conclusions in these chapters.

Comments on Chapter 6: Integrated Health Effects of Short-term Ozone Exposure

Overall there is a substantial amount of information from a number of scientific disciplines (clinical, epidemiology, toxicology, and pathology) on respiratory effects reviewed in this chapter . In response to suggestions of the Committee for greater clarity and integration of newer studies, chapter 6 has been expanded roughly 30% from the initial ISA version, and now encompasses 233 pages of text, 53 tables, 37 figures, and 31 pages of reference citations. Organization of the chapter is greatly improved and figure legends have been more clearly defined. As requested by the Committee, discussion of animal model studies have been more explicit in the chapter, and an improved and consistent use of the terms "adaptation" and "attenuation" have also now been followed throughout the text. Respiratory structural changes in animal models as a result of exposure to short-term O3 is now more clearly presented.

The older studies are now more explicitly developed with the results from newer investigations and a smoother presentation of the materials is now provided and that encompass both clinical and animal model toxicological, data bases. This is a significant improvement over the prior ISA version, and for which had previously been characterized by the Committee as troublesome, since in large measure the integration of short-term human clinical and epidemiological studies will likely form the predominant bases of the O3 NAAQS review.

The Chapter is divided into sections covering: respiratory effects, cardio-vascular effects, central nervous, and mortality. Sectional summaries have been better developed and provide a clearer interpretation of the data bases, with clear conclusions on possible/potential determinations of causality of a health effect resulting from short-term exposure to O3. For respiratory effects the summation supports a causal relationship between exposure and effect (pulmonary function, pulmonary inflammation). However, mortality as a result of short-term exposure, is suggested in the summation as a likely relationship, but not definitive as causal from O3 exposure. The studies suggesting a causal relationship for mortality are strong (Section 6.6, pgs. 6-193 thru to 6-233), and thus surprising that summation assigns only a likely association between mortality and short-term exposure to O3.

With respect to integrating respiratory effects section, with O3-related mortality section, would be helpful to co-reference within these specific sections the parallel of apparent susceptibilities of nonwhite populations and perhaps link a potential relationship between biologic responses and death (pg. 6-19, li.13-24 and pg. 208. li.3-23).

Additional references for studies that were published after the initial version of the ISA was prepared, and should be considered for integration into the text include the following:

a) to description in the text on pg. 6-109, li. 27-39, and also to Chp. 5, with respect to the TLR4 signaling and pulmonary response to O3, the recent report by Z LI et al, PLos One 2011;6(11):e27137, is helpful as the report clearly defines specifics and translation of the TLR4 pathway leading to ozone-induced lung injury.

b) to description in the text on pg. 6-103, li. 27-34, with respect to identification of a novel subset of lung macrophages (derived from resident intermediate type macrophages) the study by RM Tighe et al, J of Immunol 187:4800-08. 2011, reports upon a new cell-based endogenous protection available to the host from the biological response to ozone.

Several typographic errors in the text that should be corrected include:

a) Pg. 6-141, li. 2.
b) Pg. 6-201, li.1-2.
c) Pg. 6-224, li. 29.

Comments on Chapter 7: Integrated Health Effects of Long-term Ozone Exposure

Overall a number of organ system responses (respiratory, cardio-vascular, reproductive and developmental, CNS, carcinogenic, and mortality) have been reviewed in this chapter. The revised chapter now encompasses 85 pages of text, 13 tables, 5 figures, and 14 pages of reference citations. As requested by the Committee the organization of the chapter has been improved with separate summary and causality determinations for each organ system response that was reviewed.

The determinations in the summaries appear appropriate for the degrees of causality between respiratory (likely), and mortality (suggestive) and long-term exposure to O3.

An additional reference for a study that was published after the initial version of the ISA was prepared, and should be considered for integration into the text includes the following:

a) to description in the text of section 7.4.8, Developmental Respiratory Effects , on pg. 7-59, with respect to post-natal O3 exposure, the recent report by R Auten et al, Amer J Resp Cell Mol Biol 2011 (Nov.3 epub), is helpful as the report clearly defines structural changes to parenchymal lung tissues, and as well demonstrates a persistence of airway functional changes that do not regress following recovery from multi-day O3 exposure throughout postnatal to juvenile stages of lung development.

It would be helpful to provide an explanation in the text for use of the acronym “MSA” on pg. 7-84.

Dr. H. Christopher Frey

Comments on the Preface, Preamble, Executive Summary (Chapter 1), and Integrative Summary (Chapter 2)

Preamble

The Preamble is a useful component of the report. It is helpful to have a section of the report that provides a methodological overview of the process for developing an Integrated Science Assessment. This Preamble will be useful to many stakeholders. For example, this would be a nice chapter to hand out to a class as an introduction to risk assessment methodology.

The preamble would be even better if it included one or more flow diagrams of the following:

- The ISA process
- The various steps by which scientific evidence were considered
- The framework for causal determination

The preamble is a good place to introduce key terminology and to clarify concepts. An example is to provide closure on the recent discussions between EPA and CASAC on the definition of 'vulnerable' and 'susceptible.'

The preamble lays out the main sources of evidence regarding hazard identification and quantification of dose-response relationships: controlled human (clinical) experiments, epidemiological studies, and toxicity studies. It would be helpful for the preamble to include perhaps a ½ page to a page on the implications of the source of the hazard identification and dose-response data with respect to the choice of whether exposure or some exposure surrogate is needed. For example, many epidemiological studies are not based on actual exposure, but use ambient concentration as a surrogate for exposure, which is subject to exposure measurement error. Exposure metrics also have implications for developing exposure management strategies. For example, on page lxiii (line 11), 'concentration-response or dose-response relationships' are mentioned, but the preamble does not adequately explain which one is used under what circumstance. It is not just the form of this function, but also the relevance of the exposure metric or surrogate to actual exposure that should be discussed. A discussion of exposure (contact of a chemical or agent with the outer boundary of the body), dose (amount of chemical or agent crossing a barrier into or within the body), concentration (e.g., ambient concentration, or exposure concentration based on time-weighted microenvironmental or personal monitoring concentrations), and their distinctions and implications would be helpful. This issue comes up again on page lxiii, lines 18-19, in the question regarding "What is the concentration-response, exposure-response, or dose-response relationship in the human population?" there has not been adequate explanation/motivation in the preamble as to the premise of why there are three alternatives mentioned here for exposure.
Page lxiv uses the term 'susceptibility' (line 11), 'susceptible' (line 27), 'vulnerable' (line 27), and 'sensitive' (line 27). These terms should be carefully defined when first introduced.

Minor comments on Preamble

Page liii, lines 24-25: Give EPA (2005) not the title of the document, for consistency with other references cited here.

Page liv, lines 6-8: as written, this sentence is awkward. Explain what a 'counter-factual claim' is. Break this into two or more sentences.

Page lxi, footnote 4, delete 'It should be noted that' ('It… that' statements are passive and add no content).

Page lxvi, line 20, delete 'It is important to recognize that'

Preface

The preface does a nice job of clearly explaining the statutory mandate for NAAQS and review of NAAQS. The history of the NAAQS for ozone is informative. However, the last paragraph of the history omits the disconnect between the range of levels of 0.060 to 0.070 ppm recommended by CASAC and the decision ultimately reached by the Administrator. The text might also describe the request for CASAC to reconsider its advice, and the subsequent decision by the Administrator to leave the current standard in place pending the current review.

Chapter 1 - Executive Summary

There were no page numbers or line numbers for this section, which makes identifying specific passages difficult.

An executive summary should convey the basic purpose, relevant context, methods, results, and conclusions.

Although this is relatively short at about 16 pages, the document is nonetheless a bit wordy in places. An executive summary should distill the key points, and leave more detailed discussions and justifications to the detailed text that follows in the report chapters.

For example, the section on Scope could be cut in half or perhaps eliminated. It is not necessary to refer to other sections of the report for more details. It is not necessary to repeat basic ideas. For example, the first sentences of the first two paragraphs of the scope section are somewhat overlapping. The first three lines of the last paragraph on page 1 could be deleted. It doesn't matter if the type of evidence varies by pollutant or assessment if the focus here is one pollutant and one assessment; thus, delete this clause on the 5^{th} and 6^{th} lines of this same paragraph. The idea that this assessment builds on previous assessments was mentioned in the prior paragraph. And so on. The point here is that there are many opportunities to tighten the text, so that points are made concisely without repetition.

Page 2 – probably do not need much explanation of the weight of evidence hierarchy – could delete a couple of lines in the first paragraph on this page.

For the executive summary, consider deleting Figure 1-1. This figure makes sense to a scientist, but probably not to the lay public that would read this summary. If the figure is deleted, then the last two lines on page 2 can be deleted.

Pages 3-4. The discussion of background is not very useful as written. First, explain what background is and why it is needed. Then, just state what definition was used here. The summary of 'typically less than 50 ppb' is, however, too terse. Variation in seasonal and geographic background should be mentioned… e.g., 'background varies from X to Y ppb across regions of the continental U.S. in the summer' would be more informative than an upper bound of the worst case at one location.

Page 4, the section on human exposure conveys concepts but what are the key findings, results, and conclusions?

Pages 4-5, section 1.5: "the amount of O3 that is absorbed…" by what? E.g., the lower respiratory system? (something brief). The two paragraphs here are a bit wordy (especially the first) and repetitive (e.g., both start out referring to O3 being inhaled).

Page 6, section 1.6. This is written in a sort of passive way as if the ISA is something different… whereas this can be written without repeated references to the ISA … e.g., rather than state "The ISA evaluates and integrates…" state what was evaluated, and what was integrated in a more direct, declarative manner. Phrases such as 'discussed in this ISA', 'details… are provided in the ISA,' and (later) 'discussion for all relevant welfare effects is provided in the ISA' should be deleted. Although these may seem like minor wordsmithing comments, an executive summary needs to be as concise as possible, and anything that makes the summary unnecessarily long interferes with its mission of communicating main points to non-experts or extremely busy people who are not going to read anything else from this document.

Figure 1-2 is at an appropriate level of detail for an executive summary and is useful.

The subsections of section 1.6 should be reviewed carefully. For example, section 1.6.2 seems to boil down to a simple finding: "The last review concluded that available evidence was 'highly suggestive' that short-term exposure to ozone contributes to total non-accidental and cardiopulmonary mortality. More recent studies reviewed here support this conclusion. The current body of evidence supports the conclusion that there is likely to be a causal relationship between short-term O3 exposure and mortality." This paragraph might give some idea as to why the conclusion is 'likely' as opposed to simply 'causal.'… i.e. what is the source of weakness in the available evidence?

These are examples of the various opportunities for either making the executive summary more concise or more clear.

Chapter 2 – Integrative Summary

Overall, this chapter was very useful and provides a broad yet somewhat detailed overview of the various topics addressed in the ISA.

The discussion of the Continental North America (CNA) background concentration is useful. However, the text should do a better job of summarizing the key quantitative findings. It is confusing to state the lowest estimates in terms of 'greater than XX ppb'… please provide numbers in terms of 'less than XX ppb' as with the highest estimates. For what averaging time are these numbers estimated? Later text summarizes currently air quality in terms of 24-hr, 8-hr, and 1-hr averages (page 2-11, lines 11-13). Can both the background and current air quality data be provided on a consistent basis to enable comparison?

Page 2-11, lines 16-20 – is the greater variability for LA because of topography? (e.g., mountains)

Page 2-11, line 29… are emissions in rural areas making a significant contribution to O3 in those areas? The summary tends to make statements that are factually correct as written, but that may not be very informative because they tend to be laundry lists without any findings or conclusions regarding relative importance. Likewise, lines 31-33… which of these factors are important? Can they be listed in order of decreasing importance?

Page 2-12, lines 20-21. I could not figure out the transition from the prior text to this sentence. Perhaps leading off with 'For example,' would help.

Pages 2-12, 2-13, on avoidance behavior. Page 2-12, lines 29-30 seems to state speculatively that there 'may be changes' in behavior to avoid O3 exposure. The topic is then dropped but re-emerges two paragraphs later with a more definitive statement that 'air quality alerts… induce reductions in outdoor activity…' Thus, the degree of confidence in this finding seems to vary from one page to the next. It may be better to start with a lead paragraph for Section 2.4 that merely states what topics are addressed, and provide the evaluation, findings, and conclusions for each topic in a self-contained paragraph on that particular topic, to avoid confusion. The paragraph on page 2-13 seems to trail off with some highly jargon-laden text about 'biased towards the null.' This highly technical phrase raises a question – who is the audience for the integrative summary? Could this be stated without so much jargon?

Page 2-13 … after reading this paragraph, I could not figure out what the finding or conclusion is. E.g., "To the extent that…" follows a statement that implies that the extent is not very great. Thus, what is the conclusion about whether the ambient monitor concentrations are 'representative'?

Page 2-14… lines 6-8. Is wintertime exposure of significant interest? If not, why mention it in the integrative summary? This summary should focus on key points.

Page 2-14, lines 15-24. Some mention should be made here to clarify what the typical exposure surrogate is in epi studies used here – i.e. fixed site monitor ambient concentration?

Page 2-14, line 25… after 'inspiration'? … does this refer to 'inhalation'?

Table 2-1… are there clear statements of the conclusions for health outcomes such as "lung function"? What is given here is a lot of text but there is no statement as to which of the five-levels of the weight of evidence for causality fits here (e.g., inadequate to infer a causal relationship, not likely to be a causal relationship, suggestive of a causal relationship… etc.). Alternative, explain in a footnote as to why there is no reported level of weight of evidence for causality of many of the listed health outcomes.

Minor Comments on Executive Summary

Page 2-6, line 27: 'similar' rather than 'the same' … arguable, some of the VOC species differ and there are differences in specific elementary process that are part of the chemical mechanism. However, there are also substantial similarities in the behavior of these mechanisms.

Page 2-7, lines 2-3: as written, the phrase ‘intensity and spectral distribution of sunlight’ is incomplete. Presumably, except for sun flares, the sun is producing some consistency in the intensity and spectral distribution of its emitted light. The intended meaning seems to be ‘intensity and spectral distribution of sunlight reaching the lower troposphere.’ Lines 4-5: ‘processing on cloud and aerosol particles’ is awkward…. Processing ‘on’? by what? Should be rewritten.

Page 2-8, line 31, insert ‘and’ at end of line

Page 2-10, lines 7-8… should rephrase as “Ozone monitoring is required at SLAMS sites…”

Page 2-26, lines 13-14: this sentence is awkward, but probably can be deleted.

Page 2-30, line 21 ‘studies also attempted…’ this is very awkward. A study is not an animate person, and thus cannot attempt anything. It is more appropriate to state ‘studies were conducted to…’ Similarly, next sentence, ‘These studies did so by conducting…’ should be ‘These studies involved…’

Page 2-31, lines 2-4… this is very awkward and doesn’t make sense as written. The intended meaning seems to be ‘Examination of at risk populations is useful information for assessing an adequate margin of safety when setting a NAAQS’ or something like this.

Page 2-31, line 7 ‘small number’ but ‘both’… is the number two? Would be less confusing to just say so.

Page 2-32, line 25… awkward, this text is not parallel.

Page 2-33. Lines 10-11… should be made clear as to what ‘concentration’ is being used – e.g., from fixed-site monitors, not personal exposures?

Page 2-46, lines 8-12. This text is from the figure caption and should be deleted here.

General format comment

It is confusing to the reader when a figure appears in the middle of the page preceeded by a horizontal line, yet followed by additional text. The horizontal lines are used to denote separation between sections, so when such a line appears before a figure, the reader may conclude that the text of that section has ended. Since the text that follows has no header, this raises doubts. A way to solve this is to put all figures at the top of the page on which they appear, so that no horizontal line is needed to separate them form the prior text. Also, avoid having only 2-3 lines of text at the bottom of the page under a figure – it is easy for the reader to think this is part of a caption.

Dr. Judith Graham

General Comments Not Specific to A Charge

1. The ISA is greatly improved. The hard work is obvious. Thank you. There will never be a "perfect" document, but having said that, some significant improvements are still possible.
2. This comment is, unfortunately, identical to the comment I offered on the first ISA draft. The database for O_3 is extremely large and complex, requiring an unusually high degree of insight to describe and interpret well. I am concerned about whether this draft has had adequate external input and peer review. Eight of 27 authors are external; 4 of 14 (previously) 1 of 11 contributors are external; and 10 of 41 (previously 10 of 35) reviewers are external. This should not be interpreted as a criticism of the EPA staff involved. I know many of them and fully recognize that while several of the EPA staff are internationally recognized experts in O3, most do not have scientific expertise in this area. Thus, external experts play a major role for insuring the quality of the ISA. I also know several of the extramural scientists involved and have great respect for them. The CASAC Ozone Review Panel has a collection of experts, but the magnitude of the database is quite large and, at least for myself, I don't claim knowledge of the details of every key toxicology paper. A broader collection of external experts would offer greater assurance that the original papers have been critically interpreted correctly. This is even more important due to the brevity of the descriptions of many of the papers. As a first step, I recommend listing the authors, contributors, and reviewers according to the chapter they addressed, as was done for the 2006 AQCD. It was clear in the 2006 AQCD that the authors, contributors, and reviewers represented an array of world-class experts (EPA and external). As a second step, I recommend using additional external experts to assist in making revisions to the ISA and reviewing the next draft prior to the document being reviewed again by CASAC.
3. Great progress has been made on avoiding the artificial separation of "old" vs. "new" literature. However, it is possible and desirable to go further. To this reviewer, the only important separation is whether the conclusions of causal determination have changed with new information. Otherwise, all separation could be removed and save space at the same time. An excellent example of the problem with the artificial separation is 7-30 L19, the summary and causal determination of chronic respiratory effects. The last sentence of this crucial section says that "The results for the CHS (whatever that is) described in the 2006 O3AQCD remain the definitive line of evidence." If it's definitive, describe it, don't ignore it. Another good example of a problem is on 7-58 L19 ff. This says that only the old information is discussed if new information is not available. This restricts understanding of the weight of evidence. Another way of conceptualizing this is to think about 2 review cycles from now. O3 research is decreasing, so in 10 years there may be no "new data". We all know that there still is risk, but the 2021 ISA will need to describe all the old information *or* have a 1-page ISA referring the reader to the 1986, 1996, 2006, 2011, and 2016 documents. If this separation is an attempt at brevity, it didn't work. The ISA could add all the old relevant studies and still be shorter, or at least not lengthened. The

challenge is dealing with relevance and approaches to provide the details to support the conclusions offered.

One approach in the introduction of each section is to briefly describe the type of effects under discussion and the CURRENT (i.e., this 2012 ISA) causation summary statement (e.g., suggestive of a causal relationship). Then briefly state whether the new evidence strengthened, weakened, or changed the causation summary from the 2006 document. Then the following text would provide the evidence for the current causation statement, independent of the year of the research. There is no need for a lot of terminology like "recent" or 'new". If somebody really cares, it will be obvious from the date of the citation.

4. Concentration, exposure, and dose need clarification of definition and then need to be used consistently. For example, consider using Zartarian, Bahadori, and McKone, JESEE, 2005:15, 1-5 http://www.nature.com/jes/journal/v15/n1/abs/7500411a.html . This paper is a summary of a WHO effort that was also adopted by the International Society of Exposure Science to standardize exposure terminology. The first page of Chapter 4 has a good explanation and at some other place, the appropriate sentence from this reference is used for the word exposure. However, later it gets confounded with dose and with concentration x time x ventilation.
5. Several of the figures are very small, making it very difficult to read them.
6. Several of the figures are more than a page removed from the text discussion, making them difficult to follow.
7. Research needs pop up in several places (e.g., 4-32 L2; 6-20 L36) and should be deleted. It is necessary to have an all-or-none approach to research needs.

Chapter 1: Executive Summary (no page or line numbers in text)

General Comment

1. The level of detail and length are reasonable for an executive audience. However, the text is basically a shrinkage of the summaries from each chapter, rather than an executive summary. Consider asking what executives what to know (or even asking them). It is likely that they want to know what are the effects of O3 under ambient exposure conditions, what are the lowest exposures that cause what effects, what populations are most at risk, and what are the health impacts of those effects. Details of atmospheric chemistry (other than related to PRB), dosimetry, and mode of action are peripheral. Notice I said peripheral to the bottom line; they are important underpinnings. Another approach is to conceive a 5-minute presentation (5 ppt slides) to an executive audience and use that as guidance to revise the executive summary.

Specific Comments

1. Section 1.3 is labeled Atmospheric Chemistry and Ambient Concentrations. However, no concentration information is provided, except for background in the last paragraph. Consider deleting the concentration part and including it under exposure.
2. Section1.4 is labeled Human Exposure.
    a. If a policy maker asked a question about exposures that people (average and "at risk" populations) encountered and the answer had to be non-technical and accomplished in less than a minute, the text would be different.

b. The first paragraph is misleading. Specifically the text mentions indoor exposure as apparently equivalent weight to outdoor exposures.
c. Try creating a text that answers the following questions:
    i. What is the non-technical definition of exposure? This is important because I expect that many non-scientists would think more in terms of ambient concentrations.
    ii. What are activity patterns, especially indoors vs. outdoors? This would include exposure durations as well as activity patterns (where is the person and is the person exercising)
    iii. What are daily patterns of exposure (e.g., higher at certain times of day)
    iv. What groups are most "at risk" because of exposure. What puts these groups into a high exposure (or dose) and hence higher risk category?

3. Table 1-1. I have no comments on the table, per se, since it is just a summary of the text. However, please revisit the concept for the table. The current table has a lot of space for "conclusions from previous review", but only the causation class for the 2011 ISA. It is valuable to tell an executive whether the previous conclusions are stable or have changed. If stable, does the new evidence make them even stronger? The most important thing is what the 2011 says. Consider having the longer description under conclusions from 2011 and then under conclusions from previous review just give the class, such as causal. If you keep the text as is, look carefully at the table. Under short-term CNS, it does not give the causal classification for previous review.
4. Section 1.6.4.
    a. The first sentence says that "an examination of populations… allow for the NAAQS to provide an adequate margin of safety…" This is arguable and is a science-policy or policy question and therefore should be deleted as not appropriate to an ISA.
    b. High-end exposure is not even mentioned. It must be added. For example, "outdoor" kids are more at risk than all kids. Same thing for "outdoor" workers. A person with a genetic susceptibility who stays indoors with air conditioning (and perhaps even without air conditioning) is not at risk. A healthy person who does heavy exercise outdoors when O3 is high is at risk.
    c. What is the basis for saying we aren't sure whether COPD puts people at risk. I know that the human clinical database doesn't say they are more responsive. However, since their lungs are already compromised, a small impact may have greater consequences.
    d. As a minor point, naming the genes is far too much detail for an executive summary.
5. Section 1.6.5 This says concentration-response. This is overly simplistic since exposure-dose response is the important metric. Also, this paragraph focuses on epi, but it is equally relevant to controlled studies.

Minor Comments for EPA's consideration, but not needing discussion at the meeting

1. Text under Figure 1-1, para 1. It says "cumulative" exposures. Fine. However, this would be true for acute exposures as well, which are more relevant to human effects.
2. Section 1.6.3 says emerging evidence, but evidence is emerging everywhere, not just for these categories.

Chapter 2: Integrative Summary

Specific Comments

1. Whole chapter. Use consistent definitions of the terms concentration, dose, and exposure. For example 2-32 L6 refers to exposure-response, whereas 2-33 L11 is concentration-response, although both are referring to epi studies.
2. 2-1 L16-19 Delete "newly" because the chapter summarizes the information available; perhaps it emphasizes the new, but it is not exclusive to the new. Also, delete "policy-relevant...assessment." Insert NAAQS.
3. 2-1 Consider deleting the whole section. It adds nothing and actually is misleading. All the questions say "new scientific information". However, both old and new are used. Some of the old data forms the most important bases of the NAAQS.
4. 2-5 L32 Add "exposure-response" to the list.
5. 2-14 L18. This says low personal: ambient correlations may tend to "obscure the presence of thresholds...". Since thresholds are an important policy-relevant issue, the wording should be more precise. For example, consider adding "if they exist" after "thresholds".
6. 2-17 L9ff. The homology section needs significant expansion. Although the concepts of animal to human extrapolation are there, they are obscured. For example, there is more complete discussion of some of the MOA (including details of lung biochemistry and reactions) than on the underpinnings of extrapolation. The last sentence credits animal tox as a tool in mechanistic and cause-effect. True. However, one of THE most important values is omitted: indication of the range of O3 effects (e.g. lung pathology). Also, add the value of their contribution of MOA; this underpins WOE of causation in human studies. Since this section in the Chapter 5 needs beefing up, the changes there could be followed here.
7. 2-17ff Section 2.6. Indicate the approximate length of exposure for the animal tox studies (e.g., short-term, long-term). It makes a huge difference.
8. Table 2-1. Given its nature, this table will be used a lot. Therefore, precision becomes more important.
    a. I reiterate my concerns about the artificial separation. For example, if the 2006 conclusion is not repeated under 2011, does that mean it is no longer a conclusion? Sometimes the 2011 column says "recent studies" and sometimes it considers all studies (e.g., "collective body"). The current descriptors create confusion about the whole body of information (underpinning the NAAQS) vs. the new information that taken *alone* would often be too weak to serve as a basis for the NAAQS. Consider emphasizing the 2011 conclusions and then more briefly indicating where the 2006 conclusions were different. I realize your terminology changed, but this can be dealt with.
    b. When concentrations are given, it should be clear whether they were the lowest concentration tested. As examples (I have not listed all of them):
        i. 2-18 airway hyperresponsiveness 2011. Says effects at 80 ppb. Were lower concentrations tested and had no effect. Also, typo on "health adults". Also, delete "suggesting a genetic component." This phrase also modifies the humans

mentioned in the same sentence. Also, some kind of genetic component is likely to be involved in everything.

ii. 2-18 pulmonary inflammation, 2011 column. It says concentrations less than 73 ppb. This could be 0.

c. When concentrations from human clinical studies are given, please state whether the subjects were exercising or not. For the very low concentrations, state whether the

d. 2-19 pulmonary structure and function 2006. Add, ",some of which were irreversible," after "structural alterations"

e. 2-12 bottom right. This says that animal tox shows effects as low as 500ppb. Moffatt et al 1987 showed inflammation in monkeys after prolonged exposure at 400 ppb (see 1996 CD).

9. 2-20 ff. The whole section on respiratory effects has to be revised to clearly indicate whether the human subjects were exercising or not. Sometimes, it is indicated and when not stated the assumption is that no exercise was included. However, this is not the case.
6. 2-31 L2ff. The sentence says that "an examination of populations… allow for the NAAQS to provide an adequate margin of safety…" This is arguable and, in any case, is a science-policy or policy question and therefore should be deleted as not appropriate to an ISA.
10. 2-30 Section 2.6.7.1 This would be a good place to define sensitive, susceptible, and at increased risk, especially since all these terms are used, somewhat interchangeably throughout this section.

Minor Comments for EPA's consideration, but not needing discussion at the meeting

1. 2-5 L16-17 Delete "or doses" Without doing dosimetric extrapolations, this isn't possible to tell.
2. 2-13 L24 Careful. I define "preliminary" as something in the abstract stage. If this is true, fine. If not, then revision is needed.
3. 2-13 L29. I doubt if dose-response functions were used, using the proper definition of dose.
4. 2-15 L7. Careful about using the word lung. Stick to the accurate terminology and say LRT or RT. L9 also needs clarification. The alveolar region is part of the respiratory tract. Maybe add the word "more" before "into".
5. 2-15 L19 Change "prevent" to "reduce".
6. 2-15 L26ff. Careful, some of these are effects (e.g., modification of immunity, airway remodeling), not MOA.
7. 2-21 L22 I think the "recent toxicological studies" to which you refer are the monkey studies. If so, say monkeys since this automatically adds weight to the findings.
8. 2-22 Figure 2-3 legend. This says that the bottom row have "subclinical". First, delete subclinical and clinical since that refers to a medical interpretation. For example, altered morphology in the bottom row and airways hyperresponsiveness are not subclinical.
9. 2-23 L35. Add "increased" before "susceptibility"
10. 2-33 L15. Add "observable" before "health response".
11. 2-33 L23. Delete "recent". Most of the studies on this figure are "old", going back to 1988.
11. Table 2-1 Editorial: 2-18 bottom, left. Should be phagocytize. 2-19, top right should be healthy.

Chapter 4: Exposure to Ambient Ozone

Specific Comments

1. The focus on exposure as related to epidemiology is appropriate, but excessive. Exposure assessment has great value for interpreting human clinical studies as well as animal tox studies. For example, how many people are likely to be exposed to levels that caused pulmonary function effects in human clinical studies? There is no "exposure misclassification" in clinical studies.
2. 4-2 L5 Delete "may" and insert "do". These specific sources are NOT important to population exposure.
3. 4-10L19-24. Some of these sentences are at odds with each other.
4. 4-12 L1. Add "in this study" after "indicate that." Reason: there are other examples of poor correlations.
5. 4-19 L1ff. This discusses CHAD, saying what it has. Fine, but what is the important information within it that bears on this ISA. The use of Figure 4-3 is very useful. What about giving some figures of outputs like indoor: outdoor activity patterns by age. How about location of kids vs. hour of day by season (e.g., shows that kids are outdoors at high O3 times).
6. 4-19 Section 4.4.2 on Ozone Averting Behavior. This focuses on how people may reduce their exposure, thereby reducing their risk. However, is aversion an "effect"? If a person alters their behavior, could this be considered "adverse?"

Minor Comments for EPA's consideration, but not needing discussion at the meeting

1. 4-5 L16. Provide a reference. The table that describes this area says no such thing. For example, L21 is definitive, whereas L23 says it's unclear.
2. 4-12 L7 this says that farm workers spend 100% of their time outdoors. Didn't they sleep indoors?
3. 4-19 L1. Delete "the" and insert "all". Reason, CHAD has all the most important ones. If you doubt that, give Tom McCurdy a call.
4. 4-19 L35. Define these codes relative to concentrations.
5. 4-29 L31. "blood dose" is not relevant for O3 since it doesn't reach the blood.
6. 4-32 L13. I am *highly* supportive of this model development. However, describing models under development is not appropriate for an ISA and it should be deleted.

Chapter 5: Dosimetry and Mode of Action

General Comments

1. This chapter has been greatly improved. In particular, there is more about homology and the MOA section has more MOA than effects. There is still room for improvement, especially on the discussion of animal-to-human extrapolation.
2. It should be integrated more with Chapter 4 (exposure) and Chapters 6 and 7 (effects) to have more of a continuum of exposure-dose-response.

Specific Comments

1. Throughout, pay more attention to the definition of terms, especially dose and RT regions.

2. As described in this chapter, exercise has a major effect on dose, and in chapter 6 exercise has a major impact on effects. They could be tied together better with a new table of exercise levels described as ventilation (L/min) and the related adjective (e.g., heavy, very heavy; brisk walking, running).
3. 5-2 L7 This says "ideally …dose…is ppmxLxh…" This is NOT the ideal. Dose rate is very important since O3 toxicity is not CxT. For example, 10ppm for 1hr is different from 1ppm for 10 hours. Also, several studies in rats and monkeys have shown that intermittent exposure can be more toxic than continuous at the same C. This should be revised to talk about how concentration is different from dose and there can be several ways to express dose.
4. 5-11 Figure 5-4 has males and females. Were there any gender differences?
5. For the most part, the figures are pertinent and useful. A figure of the effect of age would be VERY useful to describe p5-14 discussion of age. Fig 5-5 doesn't add much to a take-home message.
6. 5-13 L12. This says mode of breathing "may not be biologically significant." The rationale for this is not clear and actually is not true as written. NP scrubbing removes a significant amount of O3. Also, the switch to oral-nasal breathing corresponds to exercise level and that redistributes the dose pattern to reach deeper into the lung, with different cell types.
7. 5-16 Summary. Add the concepts of the impact of age, gender, and pre-existing disease.
8. 5-17 L25 is at odds with L32.
9. 5-17 Section 5.2.3. Add a short paragraph that many/most of the studies were conducted in vitro due to the nature of the necessary measurements. Then say that when in vivo studies are described, this will be specified. Some of the language (e.g., chamber concentrations) is true, but misleading.
10. 5-26 whole section 5.3. As acknowledged in many areas of the ISA, concentration, duration, and exercise level are major determinants of effects. However, the MOA section is often deficient in these details. For example, 5-27 L5, was the exposure acute or long-term? 5-27 L14, no concentration or duration were provided. The word exercising is often used—good. However, it should be modified as heavy, very heavy, etc. It is especially important to provide details for low-level human studies. For example, the Peden and Aleis (5-31 L9) had effects at 80ppb. Using a table for the details would provide this information and keep the text simple.
11. 5-26 L30. Earlier, the ISA acknowledged that effects observed at high concentrations may not occur under ambient conditions and therefore unrealistic concentrations would not be used. True. However, the study here was via an endotrach tube (unrealistic already since scrubbing bypassed) to 3ppm. There are several 2-3 ppm animal tox studies. I realize that dosimetrically, they may be within the "order of magnitude" of ambient, BUT. A MOA theoretically precedes an effect and would be more sensitive. For example, why would it take 3 ppm to change a precursor to an effect observed at 0.5ppm? I know there is a detectability issue, and in some cases the so-called MOA study only used one high concentration, but I am suspicious of such studies having any meaning. I would delete them all. However, I know you won't. So, I recommend that you have a discussion of the concentration story, with additional warnings about in vitro not having any homeostasis or any real dose metric. That would at least place these studies in a better context.
12. 5-27 L31. This says that symptoms "led to" spirometric changes. Question- did one cause the other or were they concurrent? This is an important distinction because kids have spirometric changes, but no symptoms.

13. 5-34 Section on barrier function. Add a brief comment about time course since this will be important later to epi and other animal studies. Also, please be very clear about whether the study of permeability was from lung to blood or blood to lung. In many instances it is clear, but not always (e.g. 5-35 L8).
14. 5-34 L2 and L12. Consider deletion of Abraham et al and Foster and Freed studies. They were via an endotracheal tube, so have no C-R interpretation. I realize this is supposed to be MOA, but as discussed in the ISA and above, concentration matters and there are other studies that show similar effects.
15. 5-36 Section 5.3.5 Bronchial muscle sensitization. Bring out the story of the time line since this could have a bearing on epi time lag. The information is there, but "buried."
16. 5-45 L32ff. This is too much of a stretch for a MOA. First of all, the effect of O3 on testicular and sperm function is very uncertain at this time. Then in vitro studies not even using O3 are cited as "one mechanism." This implies there are several mechanisms. This whole paragraph should be deleted as being too speculative. In the main text where these effects are described, you can say that the mechanism is unknown.
17. 5-51 L18-19 This implies a non-linear C-R function and hence should be part of the C-R discussion.
18. It is highly likely that dosimetric differences play a significant role in interindividual variability, it terms of total dose and regional dose. However this is not brought out clearly. The story is primarily in the relationship of effects to dose and dose to anatomy, biochemistry of ELF, and respiratory physiology and then how all these factors have individual differences. For example, you could cite the background range of resting and exercising FEV1 or f and the range of responses in spirometry after O3 exposure.
    a. 5-51 L20 to 5-52 L10 True, but this has no relationship to interindividual variability as written.
    b. 5-52 L11 ff. True, but how is this related to dose.
    c. 5-52 This summary paragraph needs to be revised based on the foregoing comments.
19. 5-57 Section 5.4.2.2 Pre-existing disease. This section of 5 pages slips too far into effects and what will come later in the chapter on susceptibles.
20. 5-65 Section 5.4.2.5 is named Attenuation of Responses.
    a. Please define attenuation here at the beginning. Also, the first paragraph correctly notes that attenuation happens in lung function and symptoms. However, the fact that changes in other endpoints persist in the presence of such attenuation is not mentioned until later. The first few sentence should be introductory and give a "story", which is then explained further below.
    b. A possible unmentioned mechanism for the persistence of some short-term effects and chronic effects is attenuation of PF. For example, rapid shallow breathing reduces O3 dose to the distal RT. With attenuation of this PF response, the distal RT would receive a greater dose. Thus, attenuation is not necessarily a benefit, and could even be considered adverse.
21. 5-57 This is 23 lines about co-exposure with particulate matter. However 4 lines are devoted to a VERY unrealistic study with nanotubes (the dose of nanotubes was silly high). This study should be deleted to keep the focus on interaction with ambient PM.
22. 5-65 L4ff. This is an accurate description of attenuation of spirometric responses and symptoms. Later, the ISA explains that concurrent damage occurs. This should be briefly clarified here to avoid the impression that attenuation is a benefit.
23. 5-67ff Summary. This will be read more, making precision of language more important.

a. 5-67 L27 Insert “some” before “mechanisms”
b. 5-67 L28 says “may”, but figure 5-10 says “contribute”. The figure legend should have “some” before “factors” and “likely” before “contribute”.

24. 5-68 L1ff. This introduces the section on homology and sensitivity. However, the text is split into dosimetry and homology of response. More importantly, the pieces are not the point of the material to follow. The title should be changed to say something like “Extrapolation from animals to humans”, since that appears to be (and should be) the emphasis of the section and better describes what is to follow. The first paragraph should be clarified to indicate the value of extrapolation (mechanism, biological plausibility, cause-effect, and identification of range of effects). Then discuss that the overarching concept is qualitative and quantitative extrapolation, with interspecies dosimetry and interspecies sensitivity being the 2 components. I think of the components as similarities and differences in delivered dose (interspecies dosimetry) and then the similarities and differences in the response to that dose (interspecies sensitivity). Homology is generally analogous to “similar”. Thus, there is a homology of lung structure (influencing dosimetry) and a homology of antioxidant capacity and cellular repair mechanisms (influencing sensitivity). Thus, I don’t understand how homology is apparently defined here as response, which has a dose component. The introductory text could be revised to say that there is solid evidence for qualitative extrapolation that if an effect is observed in an animal study, it is likely that such an effect could occur in humans if exposure were sufficient. Quantitative extrapolation (i.e., knowledge of equivalent EFFECTIVE exposures) is currently substantially more uncertain. Then get into the subsections of dosimetry and sensitivity.
    a. Generally, the tone is on the differences, not the similarities, thereby inappropriately reducing the value of the animal studies.
    b. A major reconceptualization is needed, with a slight reorganization to follow. Please see the 1996 O3 AQCD (Chapter 8) for guidance.
    c. In several places (e.g., 5-68. L2) the term “chronic functional responses” is used. “Functional” should be deleted since the most important changes are morphometric.
    d. 5-68 L4. This credits animals with enabling causative determinations. True. However, equally important is the ability of animal studies to identify the fuller range of potential O3 effects in humans, albeit at an unknown concentration. For example, lung remodeling information is derived from animal morphometry after specified exposures, which can’t be done in humans.
    e. There are several examples of comparisons of interspecies sensitivity. A good interspecies comparison can be found on Fig 9-6 in Miller et al, 1988 (paper already cited in this chapter). It shows the DOSE-response of 3 species to O3 for increased permeability. This would parallel dose comparisons in these species.
25. 5-69 L30ff. This paragraph discusses species differences in antioxidant concentrations and chemical species in ELF. Fine. However, it emphasizes the differences, without saying that net antioxidant activity is likely to be important, but is not fully understood (a lung biochemist like Gary Hatch could provide accurate input to you). Consider deleting Fig 5-11. It adds nothing to understanding.
26. 5-70 L16 Add “Even with these differences…” to the beginning of the sentence. This puts a more positive emphasis on extrapolation.
27. 5-75 L10 to 23. This is important information, but is not homology. It is age-related sensitivity. The next paragraph (L24) is OK but it should be recast as genetic influences on intraspecies sensitivity. This paragraph should be revised to avoid over emphasis on the age component (it’s important but not here unless the whole section is expanded to include intraspecies sensitivity).

28. 5-76 L3ff. The word sensitivity is used without definition. The differences in responsiveness could have been due to dosimetry.
29. 5-76 L21-30. Summary. Extrapolation is exceedingly important because it brings animal toxicology into the web of understanding of the effects of O3. So, having 1 paragraph is wholly inadequate. Other sections that have far less importance are longer. The first sentence emphasizes the limitations, rather than the strengths. Balance is needed. Where is the summary of similarities of regional dose patterns? L24-26 should be deleted (not the right place for genetic sensitivity and infant mice).
30. 5-77 L36 Add the importance of animal studies to understanding the full range of potential effects.

Minor Comments for EPA's consideration, but not needing discussion at the meeting

1. 5-6 Section 5.2.2.1 Consider deleting this section. Earlier sections have tutorials (e.g., RT anatomy) that are useful because they define terminology used throughout. However, these principles are not needed to understand the text.
2. 5-14 L15 Delete "pulmonary physiology" and insert "RT anatomy." Reason, the factors given like TB volume are anatomy not physiology.
3. Be careful to provide all units. Ex: 5-14 L20 and 5-16 L26 O3 absorbed per minute per what? cm2 surface are of LRT?
4. 5-19 Delete Fig 5-7 if you want to save space. It adds nothing.
5. In several chapter the year of the Que is study missing.
6. 5-47 Figure 5-9. Right bottom says epithelial metaplasia and "fibrotic airways". This is too strong. Replace with "fibrotic changes".
7. 5-64 L37 This study is a co-exposure study and should be relocated there.
8. 5-66 L22 Insert "some" before "responses."
9. 5-69 L29 delete "could"

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

General Comments (My focus is exclusively on the human clinical and animal tox studies and may or may not be pertinent to epi)

1. This is greatly improved, but still has a way to go.
2. This chapter is the *most crucial* since it has the information on exposure-response that will be the foundation of the NAAQS. Hence, it deserves the greatest attention to precision and clarity. In my view, five changes are essential to this goal. They are:
    a. Eliminate the distinction between "old" and "new" studies. This problem was reduced in this draft, but is still inadequate. Reasons follow.
        i. The NAAQS is based on the scientific evidence, not the recent evidence. There are egregious examples in which an "old" study at 0.12ppm is given short shrift, but a "new" study at .7 or 1ppm gets a lot of space. Thus, to serve the purpose of the ISA, the science needs to be described, independent of date.
        ii. The separation causes unnecessary duplication of the explanation of effects. The result is to decrease understanding of the reader.
        iii. The fix is relatively easy; it is editorial.

b. Clearly and succinctly explain the lowest effective exposures in human clinical studies. All the information is in the text, but it needs to be drawn together in ONE summary table. This table should answer the question, "What is the lowest exposure that causes changes and what are these changes?" The table would focus exclusively on concentrations from the lowest tested (probably 40ppb) up to 80ppb only. Given the importance of duration and ventilation, possibly have 1 table that only had one duration and ventilation and different ppb's to permit comparisons (e.g., several studies from several labs with similar protocols reached similar conclusions). Another table would have other V's and T's if that helps answer the question. One column would be ppb, spirometric changes, symptom changes, hyperresponsiveness and inflammation. The table would indicate % changes and whether they were statistically significant and, as appropriate, what % of the subjects was most responsive. This would also permit a reader to see the whole of a study in one place and not have to read different sections of the text to see the correlation of spirometry, symptoms, inflammation, etc. I don't want to prescribe a specific table, but one had to wade through a lot of information and a lot of summaries to answer the key question about lowest effective exposure.
c. Describe the severity of the effects observed. This is briefly mentioned for spirometric changes, but not discussed for symptoms and human clinical inflammatory changes. For example, what are the symptoms and what is their impact? Since inflammatory changes are now observed at exposures lower than those that cause spirometric changes, a much fuller explanation of impacts is needed. Such a discussion is needed to scientifically support later decisions on adversity.
d. Describe the relationship of human clinical study protocols to people in the real world. For example, typically only mild asthmatics are subjects, but the real world has a greater range. There are limits to children's studies. What do these exercise levels mean? What population groups are likely to have exercise levels equivalent to those of the human clinical studies observing effects at very low concentrations. How does the duration of exposure, with intermittent exercise, relate to the real world?

3. The discussion of animal tox studies is totally ***inadequate*** and does a disservice to understanding the effects of O3. There are 4 major problems:
    a. Lack of tables. It is ***totally unacceptable*** to cross reference tables in the previous CD's (even the 1986 one is mentioned) and then add a description of new studies, some of which are less important than others buried in old CD's. Nobody is going to sit down with 3 documents in front of them. As stated in the text, rat studies may dosimetrically underestimate exposure compared to humans. This makes rat studies at several hundred ppb very relevant. Therefore, morphometric changes or immune-related changes from exposure of rats to 300 or 400 ppb may be very relevant to humans, but impossible to study in humans for ethical reasons. I recognize the desire to keep the ISA short, but it isn't. For example, many pages are devoted to mechanisms of uncertain relevance, while key animal studies showing the range of effects are buried in an old document. Pages are devoted to effects of uncertain relevance (e.g., neuro) while only a few paragraphs are devoted to lung remodeling; probably because of date of the study. To conserve length, the animal tox tables could be truncated to below a specific exposure (e.g., .75ppm) and the critical effect ones could be chosen (e.g., inflammation, morphology, a few others).

b. Some text descriptions are quite good if supplemented with tables; others are woefully deficient. For example, lung remodeling is extremely important. The Section 6.2.3.3 (6-79) is under the larger text of pulmonary inflammation, injury and oxidative stress. The forgoing material is primarily on inflammation. The text describes several dozens of studies on lung morphology. The old studies are cross-referenced to old CD's. A quarter of a page is devoted to a listing of dozens of references for "new information on underlying mechanisms." The animal tox literature provides a much broader understanding of the time course of inflammation and structural changes that would be of significant concern if it could be clearly shown that they would occur in humans.
c. Some animal tox sections have tables with the new studies only. This gives a biased picture. It does, however, make fixing it easier since it would be an editing merge with the tables in the old document.
d. The description of morphological changes is inadequate. It is more than "lung remodeling". I did a search and couldn't find Type 1 (or Type I) cells or Clara cells. Describe the hyperplasia and metaplasia and what it might mean. There are multiple papers and summaries (e.g., 1996 AQCD). For example, consider the discussion section of Plopper et al 1998, referring to monkeys exposed at rest to 0.4 ppm for 2 hr. (keep in mind that it takes about 0.5ppm to cause spirometric changes in at rest humans).
e. "The protocol for studies of human exposure produces significant epithelial necrosis in very short time frames in distal conducting airways of non-human primates."

4. The term "tolerance" is used several places, sometimes in the same sentence with "attenuation," (e.g., 6-2 L22, 6-22 L24, 6-102 L27) suggesting that it is being used synonymously. The terms are NOT synonymous. For O3, the term tolerance is traditionally used for animal studies in which a lower concentration is used to protect against a VERY HIGH (e.g. over 10ppm) O3 or some other chemicals. Thus, it has no place in this ISA and should be deleted throughout.
5. There are several examples of duplication to the MOA section of Chapter 5. In some cases, such duplication is useful when summarizing the causation elements. However, in other cases it is superfluous (e.g., 6-60 L1ff). Cross-referencing Chapter 5 should be done more frequently.

Specific Comments

1. Throughout for the human clinical studies, it is essential to better characterize the degree of exercise because it has a major influence on the exposure-response. In some cases the word exercise is not used at all (e.g., 6-4 L31), the word "exercise" is used without modification (e.g., 6-6 L17), the word exercise is modified by an adjective like very heavy or the actual V_E (e.g., 6-5 L23) is given with no indication of what it means. One approach would be to have a table at the beginning of respiratory effects that describes the adjective (e.g., moderate), the corresponding V_E, and the corresponding description (e.g., brisk walking; running a race). Then the text could use the word exercise with the adjective modifier and the tables (to be added!!) could have the V_E.
2. 6-2 L4 ff Add symptoms since they will help define "adversity."
3. 6-2 L34 This says that infection in early life is associated with asthma incidence. True. I thought it was also associated with COPD incidence; please check on the accuracy of this statement.

4. 6-5 L31. This is not "actually a measure of exposure", according to the definition used in chapter 5. It may be typically used as a surrogate of dose. Perhaps, say that the product of CVT has a huge influence and avoid the words exposure and dose.
5. For the 6.6 hr. exposure, add a short discussion about the time course of effects. For example, was the effect observed at less than 6.6 hours? This time course could be important since very few people would be exposed in the real world for 6.6 hours.
6. 6-10 L33ff. this is a very good discussion of the bottom line of an extremely important group of studies. It is only missing a correlation with symptoms, an important element since it was included in these studies and is part of the definition of adversity.
7. 6-56 Section 6.2.1.3 Toxicology section. L22. The Wiester study is the effects of temperature, as well as the time course of functional changes over 5 days. The Tepper et al 1989 (look at Ch. 5 for full ref) is the one with lack of attenuation for structural changes.
8. 6-69 Tox section. The organization of this section should be revisited. Lung lavage studies should be more in one place.
9. 6-79 L24. This is several dozen references, with no explanation other than "new information regarding the underlying mechanisms." Therefore, these lines have no benefit. If the studies are important, they should be in the MOA section of Ch. 5.
10. 6-81 Table 6-17. Good table, but it needs some clarification. Specifically, the Harkema et al 1993 needs expansion. There was also an exposure to 0.3ppm with greater impact. The observations need to be expanded to include the interstitial changes and more details of the changes themselves. All the observations need to be consistent in level of detail offered. For the Hyde et al, 1992, what were the morphometric changes?
11. 6-83 L4-9. This is a good example of excessive duplication (significant explanation of gene interactions at 1ppm, with cross reference to chapter 8) that offers no useful information beyond what has been known from the older studies that are ignored.
12. 6-106 L33 This needs to be clarified. Indeed, there is no epi evidence of mortality from infection. However, in the mouse studies, mortality was an *indicator* not an endpoint to be replicated. So, when the text says "little compelling evidence"—evidence for what?
13. 6-140 L34ff. This is the summary section and this area describes the human clinical studies at 60ppb on inflammation. This discussion needs to be expanded to discuss severity interpretation.
14. 6-175 Section 6.3.3 Toxicology. This section is "formally" split into old (6.3.3.1) and new (6.3.3.2). Although other sections often have a separation within the text, they don't formally split it. Such a split results in excess duplication. The split is of more significant concern because some of the old and new show similar effects, increasing the weight of the evidence.
15. 6-176 L3ff. What were exposure durations?
16. 6-176 L11 mentions human studies. Describe them—epi or clinical; exposures.
17. 6-176 L22 to end of section. This is speculation on the mechanism of CVS changes and is located in the old section. First, MOA belongs in Ch. 5. Second, the MOA discussion is longer than the inadequate description of the effects.
18. 6-177 ff Section 6.3.3.2 recent studies. This has a table, which is OK at the end of the section. However, one can't read the text without reference to the tables. For example 7-177 (L19) should give the concentration. There are other examples. The text should stand alone, to a small degree, with the details being in the table. The table should have the old studies since in some cases they show the same effect, increasing the weight of the evidence.
19. 6-182 the tox summary has more on MOA than effects. Increase explanation of effects and cross-reference Ch. 5.

20. 6-184 L15. This is a good example of the problem with truncating the description of the old data. The Tepper study was at 0.1ppm, which is considerably lower than many of the new studies described in more detail.

Minor Comments for EPA's consideration, but not needing discussion at the meeting

1. 6-7 Figure legend Panel A does not have Adams 1998
2. 6-84 L5ff. This section is labeled "Mechanisms of Injury" and is another example of excessive duplication. It should be in the MOA section of Ch. 5; only a cross-reference is needed here.
3. 6-103 L9 this is long-term exposure
4. 6-139 L11 Add the Tepper et al ref
5. 6-141 L2 typo
6. 6-143 L21. Says they "failed to demonstrate". Did they even look?
7. 6-143 L23. Describe the exposure conditions.
8. Animal tox tables throughout. The titles are not consistent. Also, some titles are misleading in that they imply a complete listing of effects when it lists only the new studies.
9. 6-81 Table. Please specify the ages of all the monkeys since a lot of infant studies were conducted.
10. 6-191 Section 6.4.2 This summary includes 3 references out of several dozens. Why were these choses for calling out?

Chapter 7: Integrated Health Effects of Long-Term Ozone Expousre

General Comments

1. The animal tox tables presented here are better here because, for the most part, they do not artificially separate the old and the new. However, they should be expanded with *all* the *relevant* studies. Also, in many cases (e.g., 7-19 L14-38), O3 effects are described in the text with no indication of the concentration or duration. This information is sometimes in the tables (but difficult to find); sometimes the study mentioned is not in the table (e.g. 7-19 L31). Basically, the text needs to have minimal info on study protocol (e.g., concentration, adjective or details about duration, species).
2. The morphological effects observed in animals should be described in more detail, with discussion of the potential impacts of such effects. For example, what exposures cause increased interstitial thickness of the CAR and what does this mean? What effects were irreversible? What is the difference between continuous and intermittent exposure over time?
3. Several developmental studies of animal pups are described. All of the key papers in this group should be examined for exposure methodology. Very young pups will be close to their mothers and absorption/reaction on maternal fur would reduce the exposure. If they were exposed on bedding, the exposure likewise would be reduced. This methodological issue should be mentioned briefly if there are papers where these variables weren't controlled.

Specific Comments

1. 7-17 L11 This is the beginning of animal tox, including the most important studies of structural changes. I say most important because they cannot be studied in humans, but for many reasons, it is very likely that humans would experience these effects if exposure was sufficient. Thus, the first 2 sentences are a major problem because they essentially dismiss animal tox because of difficulties in extrapolation. Indeed, there are difficulties in quantitative extrapolation, but they are not overwhelming. They are underexplored in this ISA (Ch. 5). It goes on to say (L16) "However, important…nonhuman primates…" This implies that only monkey studies are of relevance. That is just not true. Monkeys, rats, and other species have similar effects in the CAR, although structural details are different (e.g., monkeys have respiratory bronchioles). This whole introductory paragraph needs to be recast.
2. 7-17 Section 7.2.3.1 discusses the non-human primate studies of the Plopper group. The body of work has studies of infant and adults, and in some cases direct comparisons of the influence of age are possible. This needs to be brought out because of the great importance of age being a risk factor.
3. 7-18 L3ff This cites findings that were not statistically significant. This creates a problem since the reader is then uncertain about the statistical significance of the whole document, unless a specific statement is made. Only cite non-statistically significant studies if they are overwhelmingly important and have been examined to determine the reason. For example, if the sample size was very small, there probably was no effect. Maybe the effect was driven by one high responder, in which case, this could be discussed. Another example is on 7-40 L22 in which a statistically insignificant effect (at 1.2 ppm) is discussed.
4. 7-25 L1ff. This paragraph needs to be clarified since some exposures were acute and others subchronic. Also, it is misleading to say "protective adaptation". Indeed, there was an adaptation. But, as described in earlier documents (and to a lesser degree in this ISA), the pattern is that inflammation measures return to normal while measures of cellular remodeling and fibrotic changes increase.
5. 7-30 L9. Similar effects occur in adults so a revision is needed. Also, the first sentence begins with "irreversible morphological changes…, which in turn can influence pulmonary function." True, but it is far more than an impact on pulmonary function. You could say the functioning of the respiratory tract, which is more inclusive.
6. 7-32 L7 Says "cumulative impacts". This suggests a C x T. The tox studies (those presented and not presented) indicate that seasonal exposure can have different and more effects than "continuous" exposure, even though the C X T on seasonal was very much lower. Thus, delete "cumulative" and explain.
7. 7-38 L30. This says that the Rubes study "did not identify specific pollutants and their concentrations." Also, it appears the other 2 studies in this paragraph were similar. So, why cite them if they are essentially useless.
8. 7-39 L10ff. This section describes one O3 study and then cross references the MOA section (5-45) for support. However, 5-45 is very weak and speculative and does not offer support. For example, L 14 says "studies", but only one study is cited.
9. 7-39 L30ff This introduction to effects on reproduction is not supported by the OZONE data (a stretch to include smoker data, intimating that O3 may be similar).
10. 7-59 L4. This study is useless as an interaction study because the dams were exposed to PM intratracheally to 0.48 mg twice weekly for 3 weeks. This is an absurdly high dose. The O3-only group data would be relevant.

Minor Comments for EPA's consideration, but not needing discussion at the meeting

1. 7-18 L31. This compares the concentration of a chronic animal study to a controlled human exposure study. This is a false comparison.
2. 7-20 L30 Change "effects" to "impacts" because the effects ARE known.
3. 7-25 L8 why are acute studies here
4. 7-69 Table 7-10. The rationale for the order of the studies presented is not apparent. Also, it is labeled "key" studies. Why are studies at 3ppm "key...This is unrealistically high?
5. 7-75 Section on carcinogenic …. Cancer is always a high-attention area, requiring more precision.
    a. The word "dose" should be deleted throughout this section and replaced with "concentration."
    b. 7-76 L10ff discusses the NTP study was very well designed and had adequate power to detect changes of concern. This area has several lines (e.g. L15, L23) with phrases like "marginally significant", "some semblance of a dose-response." Trying to pull out findings that were not supported in the report is not warranted. Also, the study found no effects of 2-year or lifetime exposure of rats, but these negative data are not included. Given the quality of this study and its importance, it should be explained in detail with a table (simply copy the 1996 CD entry).
    c. 7-76 L23. What was marginally significant? Was it a minor difference? Was the power of the study adequate

Chapter 8: Populations Potentially at Increased Risk for Ozone-Related Health Effects

General Comments

1. Generally, the chapter is very good and a significant improvement. However, further improvements would be important.
2. Epidemiology studies from many countries are summarized throughout. Please add a discussion of the strengths and limitations of using such studies from other countries. I wonder to what degree the information is quantitatively (and even qualitatively in some cases) interpretable for the US situation. For example, in some cases pollutant mixtures would be very different, O3 concentrations and patterns could be different, and SES is likely very different (e.g. Low SES in China is likely to be different from low SES in the US).
3. The separation of old and new studies is totally inappropriate. It adds nothing. In some cases it is misleading and is unevenly treated. For example, 8-13 L26ff. It says that previous and current human and tox studies show age effects, but "recent … [epi]…" are inconsistent. What about the old epi? Just describe the studies.
4. Throughout, the level of detail of presentation of concentration, exposure durations, and exercise levels is uneven. Such information should be presented judiciously in the text and in more detail in tables.
5. The organization needs revision, as described in more detail below. Generally, the term "at-risk" is a good one because it is all encompassing. The organization should have two conceptual components: risk related to increased exposure and/or dose (e.g., high concentration

environments, exercise) and risk related to responsiveness to a given dose (e.g., asthma, genetics).

Specific Comments

1. 8-1 L1 Delete "suggests" and add "indicates". Interindividual variation is real, not a mere suggestion.
2. 8-1. This is a valiant effort at definitions, but falls short. Some comments:
    a. L10 and L11 add to the e.g., with some related directly to O3 (e.g. intrinsic should include preexisting disease).
    b. L 18-20 apparently has 2 "categories", whereas L23 below has 3 categories.
    c. L23-32 (I recall CASAC commenting on a proposed definition, but I can't recall it. Therefore, I'll just comment on what's here.) I support the "at risk" phraseology. I strongly object to there being 3 categories. First, intrinsic and extrinsic are *complete*, and there can be no "third". The term increased dose is indeed a risk factor, but could be a mixture of intrinsic (e.g., anatomy, physiology) and extrinsic (e.g., exercise, contact of greater concentration). It gets even worse by L29 in which a greater exposure is a separate paragraph.
    d. To me, the greatest need is to define how the "sensitivity" term of the CAA is being used in this ISA. This is reasonably well done in the first paragraph in which sensitivity is translated to "at-risk."
    e. Intrinsic and extrinsic are not used in the body of the chapter. Rather, the chapter is organized by risk factors. Perhaps the best approach is to polish the first paragraph and then discuss the complexity of the interactions of many of the factors, bringing in intrinsic (biological) and extrinsic (everything else, including higher exposure, higher dose, SES).
3. 8-2 provides good context.
4. 8-3 around L15. Insert the concept that preexisting disease can present a risk because of less reserve (i.e., the same percent change may have more impact in a person with COPD).
5. 8-10ff Children are a major at risk group, thereby requiring more precision of language. For example, the introduction basically says that the old data show effects in kids and "New evidence, summarized below, further supports…" However, the following has some old details, appropriately so. This illustrates the false dichotomy between old and new.
6. 8-10 L23. Add that kids have less symptoms than young adults.
7. 8-11 L8ff. This is a good example of the misuse of old and new data as an organizational feature. L8 implies that this is the whole of the "old" and L22 begins the new ("recent"). However, later old work is brought in.
8. 8-12 The infant monkey studies are discussed here and later. They are quite important. However, the summary focuses on the infant results ONLY, whereas the introduction to this chapter says the goal is to compare age groups. The entire set of the Plopper studies supports age comparisons, but these comparisons are not brought out here.
9. 8-12 L25 uses the term "protective adaptation", implying it is a beneficial effect. It could be argued that it is a detrimental adaptation, so omit the adjective.
10. 8-14 L1ff In the first paragraph insert the concept that older people may have less reserve, making relatively small changes have more impact.

11. 8-25 Section 8.6 is called BMI and Physical Conditioning. Indeed there is a link. But having them together implies that physical conditioning "may also affect the risk…" (L30). The text doesn't demonstrate that physical conditioning is a risk factor. It could be argued that exercise in the presence of O3 (see later in this chapter) is a risk factor. Please clarify.
12. 8-28 L20 ff. Was there an interaction with SES?
13. 8-29 L29. This says that smokers were at "less risk." They definitely were less responsive, but this is different from "less risk." 8-30 L21 alludes to this by saying "pseudo-protective." The story needs to be consistent.
14. 8-30 Section 8.1 is Heightened Exposure. It should be expanded to be exposure and dose. At present, it focuses on outdoor workers and lack of air conditioning in some households. It does not mention exercise, although that is a major risk factor (e.g., in clinical studies, it takes 500ppb to cause spirometric effects if the subjects are at rest). It does not mention children although they are outdoors in the summer afternoon exercising (a triple risk: kid's developing lungs, encounter high O3 due to time of day, and exercise (i.e., greater dose). The concepts need to be laid out in the first paragraph
    a. Concentration response important
    b. A person has to be exposed; most people spend 90% (get actual estimate from OAQPS) indoors where concentrations are lower, even without air conditioning.
    c. Exercise increases dose
    d. Therefore, people who are outdoors exercising, especially at times of day when O3 high are at greater risk.
    e. Then have the text expand on these concepts. Outdoor worker and air conditioning discussion is generally fine, but other elements are not discussed.
15. 8-31 L34. This says that "increased exposure to outdoor air does appear to confer additional risk…" This needs to be stronger. There is no doubt that increased exposure, etc., really does confer additional risk. The exact concentration and duration can be argued, but this generic statement needs to be stronger.
16. 8-33 L22ff. This is a summary of heightened exposure. It needs a total revision since the only emphasis is outdoors.
17. 8-33 L27. First, make this a new paragraph since it is a different concept.

Minor Comments for EPA's consideration, but not needing discussion at the meeting

1. I couldn't find a definition for HA in this chapter, but maybe I wasn't looking hard enough. Since it is used frequently, please make sure it's defined here.
2. 8-10 L1 Delete "recent" because it implies that maybe there is an older literature that you aren't describing.
3. 8-11 L18 Insert "lung" before "regional"
4. 8-12 L18 Change "nasal airways" to "respiratory tract".
5. 8-14, L5 and 8-15 L28. Both place say that diminished symptoms allow them to "withstand" increased O3. This language implies this is a benefit. However, it could well be a detriment since they would not seek relief by avoiding exposure.
6. 8-27 L6. Clarify that this effect was with O3 exposure.
7. 8-32 L22. Delete "may". There is no doubt about it.

Dr. David Grantz

Chapter 9: Environmental Effects on Vegetation and Ecosystems.

This Second External Review Draft ISA provides a thorough and scientifically valid presentation of the current state of the science regarding effects of tropospheric ozone on vegetation. I appreciate the reorganization and improved clarity in response to CASAC comments on the First Draft ISA.

The document appropriately captures new information (since the last AQCD) on the molecular and genetic underpinnings of ozone impacts, on available comparisons of chamber-based and more recently published chamberless exposure studies, and the results of several meta-analyses that provide an integration of the previously available information.

The physiological and biochemical mechanisms of ozone impact are presented in sufficient detail to demonstrate plausible mechanisms of injury, without delving unnecessarily into the still poorly characterized signaling cascades that mediate them. However, as noted previously, the mechanism of ozone impact is predicated upon a "sensing" of ozone by the plant which does not describe the process as currently understood. Further revision is suggested. For example, the process described on page 9-10, e.g., lines 18 and 28, and page 9-36, line 29, is much more accurately described on page 9-17, lines 26-30. This latter framework should be used throughout. Also as noted previously, it is important to consider that gene expression is itself a response, contrary to page 9-11, lines 27-28 and page 9-19, lines 20-32. Differences in genomic responses between sensitive and tolerant plants may reflect differences in ozone uptake or detoxification, or they may fundamental differences in gene regulation. It will likely become important to distinguish these. The new information on proteomic differences is an important contribution of this document. To further highlight this contribution, a distinct Conclusions section could be added to Section 9.3.3.2 (page 9-22).

The available knowledge that is most policy-relevant with respect to setting of a Secondary Standard remains the set of yield-loss relationships described in the previous AQCD. These were derived from OTC (i.e. chamber) studies during NCLAN, NHEERL and European OTC studies. The current document appropriately evaluates and ultimately reaffirms previous conclusions based on these studies:

- That ozone impacts on vegetation occur at current and potential future ambient concentrations,
- that exposure-response relationships remain the best available means of quantifying and predicting the impacts,
- that the exact mathematical relationships that best describe these relationships remain unclear although cumulative indices that emphasize high concentrations may outperform means,
- that flux-response relationships including temporal trends in plant susceptibility are promising but not yet sufficiently developed.

An important aspect of Chapter 9 is the inter-comparison of the chamber and chamberless exposure-response data. Using data from the Free Air systems in Urbana IL and Rhinelander WI, the document shows that previous concerns that hypothetical "chamber effects" had skewed and potentially overstated the effects of ozone on vegetation, are in fact not significant. This is shown clearly by presenting the convergence of yield predictions based on exposure-response relationships from the two types of systems, and on relative yield reductions. A potential improvement to the presentation could be achieved

by further consolidating this material along with the meta-analyses, which are now scattered among the description of the exposure technologies (Section 9.2), the results from each type of exposure (including meta-analyses, Sect. 9.4) and the results of the explicit comparisons of the contrasting exposure technologies (Sect. 9.6).

The mathematical definition of the exposure indices (page 9-106, line 14-20) occurs after most of the discussion of them. This could be moved to precede the discussion. Section 9.5.3.1 is poorly focused, and the conclusion that ozone peaks are important is somewhat obscured. The legend for Figure 9-12 is unclear (what is "Mean diurnal."? and what is "flux cutoff threshold"?). In the legend for Figure 9-18, should define IQR as Inter-Quartile Range. In 9.6.3.5, the reference to Tables 9-18 and 9-19 should be corrected to 9-17 and 9-18.

In Table 9-17, the first reference to Grantz and Shrestha, 2006 indicates that the work was done in France. It was done in the San Joaquin Valley, CA. The second reference to this study shows no location. In Table 9-18, this location is called Parlier, rather than San Joaquin Valley, CA. Clearly these should all read the same.

Effects on photosynthesis are appropriately emphasized. It is recognized that there may be direct as well as indirect impacts of ozone on stomatal conductance. However, there may be other indirect effects in addition to stomatal response to intercellular CO2 concentration, including metabolic communication following ozone attack on the mesophyll (page 9-13, line 7; page 9-37, lines 1-6). Discussion of C4 sensitivity to ozone should include a reference to Grantz and Vu, 2009 (page 9-32, lines 10-19). The mention of nocturnal stomatal conductance is appropriate given its current level of research interest, however this behavior may receive more attention than is warranted based on its prevalence and potential impact on ozone flux. The conclusion that fast growing plants with large stomatal conductance are most sensitive to ozone (page 9-82, line 1) is not consistent with the previous conclusions that the allometric coefficient of slow growing plants is more sensitive (page 9-48, line 31). This inconsistency probably cannot be resolved here, but in this and other cases in this chapter (e.g., stomatal opening vs. closing responses), obvious discrepancies should be acknowledged and whatever differences can be identified (e.g., in endpoints or species) should be noted.

Impacts of ozone on root growth are very important. This has important physiological impacts and may in future be shown to impact carbon sequestration. All available meta-analyses support the conclusion that ozone reduces allocation below ground, as noted in 9.4.3.2. The conclusions in 9.4.3.1 and in 9.4.3.2 are weak and suggest uncertainty where little exists. For example, there are clear population level explanations for the data of Pregitzer et al., 2008 that reduce the level of uncertainty in the conclusion.

The analysis of hydraulic conductance (page 9-70, lines 22-34) is somewhat confused. There is a specific quantitative relationship between stomatal conductance, leaf and soil water potentials, and hydraulic conductance, that is not consistent with the text. The abbreviation for hydraulic conductance (kl?) requires definition at first use. Sap and stem flow are not synonymous (page 9-70, line 38).

Section 9.6.3.3 attempts to demonstrate that the components of an aggregate population do not exhibit the same statistical properties as the population as a whole. While this is true, the cottonwood data in this section more clearly demonstrate that there are outliers in any population.

The Second External Review Draft contains considerable information that will be useful in development of a Secondary Ozone Standard and in providing a summary of the state of the science for multiple applications. The organization is much improved relative to the First Draft and the conclusions are sound. Attention to the above suggestions may help to address the few remaining rough spots.

Dr. Jack Harkema

Comments on Chapter 6: Integrated Health Effects of Short-Term Ozone Exposure

General Comments:

In general, the overall format for this chapter is appropriate and the text is clearly written. The authors have thoroughly reviewed the recent literature and have included the most pertinent recent studies since 2006. There are areas of redundancy, however, in this chapter and in Chapter 7 that need to be eliminated.

In some sections of this chapter, the authors spend too much time rehashing details of studies previous to 2006. Emphasis should be placed more on significant recent novel findings and their relevance to the bottom-line conclusions of short-term ozone exposure's impact on specific health effects.

Not all of the sections follow the same format. The chapter would be improved with a consistent format of presentation that includes: 1) brief presentation of the major conclusions of the previous 2006 AQCD (summarizing tables of past studies could be used); 2) focused discussions on the major studies since 2006 that have contributed new and important information to the area (references may be made to previous important studies, but only when necessary); and 4) an overall summary/conclusion paragraph(s) that synthesizes and critically evaluates the relevance/impact of these studies on the subject area.

There are a few references to studies "In Press." These should be eliminated from the discussion.

Specific Comments:

6.1. The introductory paragraph is well crafted and clearly and concisely written. It nicely sets the stage for the reader.

6.2. Respiratory Effects. The conclusions from 2006 AQCD are well summarized.

6.2.1 Controlled Human Exposure

p.6-5. Good explanation of the need for FA control exposures. The authors may want to also discuss the possible impact of ambient O3 exposure history prior to controlled O3 exposures and whether or not most studies address this issue.

Figure 6-1, p.6-7. The statistical significance of FEV1 decrements at each ozone concentration should be indicated in both graphs.

p.6-8, line 19. Since there are numerous abbreviations throughout this chapter, the authors may consider replacing "S-W" with "square-wave" throughout this section.

p.6-9, line 5. The authors may want to address what contribution each exposure scenario (triangular, square wave) makes to better understand the health effects of ambient exposure.

p.6-10, last paragraph. Clinical significance of a 6% decrease in FEV1 should be discussed here or elsewhere in this chapter (e.g., end of first paragraph on 6-11).

p.6-14, lines 20-21. Here the authors reference a decrement of FEV greater than 10% as an abnormal response. Does that imply that lower ozone-induced decrements are not clinically relevant?

p. 6-11, last paragraph. End this paragraph with a concluding statement on the clinical implication of O3-induced changes in small airways and ventilation distribution compared to the changes in large airways.

p. 6-15. At the end of the first paragraph, the authors should present some suggested biological reasons why COPD patients appear to be less sensitive to ozone exposures.

p. 6-15, Responses in Individuals to Pre-Existing Disease. Authors should provide the range of exposure concentrations and exposure scenarios used in these studies.

p.6-17. Factors Modifying Responsiveness to Ozone. In this section, it would be helpful to provide subtitles introducing the factors being discussed.

Very little new information is being presented in this section. This section should be shortened by presenting more concise statements on the major findings prior to 2006 and highlighting those from more recent studies.

p. 6-23,-24. In this summary, the authors should point out that few or no recent studies have been done in this area. Most of the information provided in this summary is based on studies prior to 2006.

6.2.1.2. Epidemiology
A lot of the discussion focuses on studies prior to 2006 that was presented in the previous AQCD. The authors may want to consider shortening the descriptions from past studies and highlighting the more recent studies.

6.2.1.3 and 6.2.2.2 "Toxicology." The titles are the same for both sections. Differences in the content of the sections should be designated somehow in the titles (e.g., 6.2.2.2 "Animal Toxicology")

The sections on Toxicology appear to follow a different presentation format than the other sections in this Chapter. Authors of this section should try to use the format used by others (see general comments). The toxicology sections could be shortened by providing more of a summary of previous findings prior to 2006 and providing more focus on the recent studies.

p.6-60, line 22. Do not include "In Press" studies.

6.2.3.3. Toxicology. Title could be changed to "Toxicology: Airway Inflammation."

p.6-84. Respiratory Symptoms and Medication Use
Some areas are redundant with previous sections.

p.6-102 The authors may want to reconsider changing the section titles to “Tracheobronchial Defense: Mucociliary Clearance “ and “Centriacinar Defense: Transport Mechanisms.”

6.2.5.4 Infection and Adaptive Immunity
Animal studies in this section are well written and concentrate on recent studies since the last AQCD (2006).

p.6-141, line 2. Reference needs parentheses.

6.2.9. Summary and Causal Determination p.6-137. Summary and Causal Determination of Respiratory Effects is very well written.

6.3 Cardiovascular Effects. P.6-143.This section of the Chapter is well presented with the most interesting new studies. The overall presentation of this section may be interpreted by some as demonstrating more than just a “suggested” causal relationship between short-term O3 exposure and cardiovascular health effects.

Summary statements should be provided for all of the subsections under the cardiovascular effects.

p.6-175. In the Summary of Epidemiological Studies, the authors may want to expand upon the statement that there is consistent positive association found between O3 and cardiovascular mortality.

6.3.3 Toxicology
p. 6-17, lines 1-13. It should be noted that the decrease in heart rate (bradycardia) and mean arterial pressure demonstrated in rats (Watkinson et al.) most likely is due to the trigeminocardiac reflex (or diving reflex), the most powerful autonomic reflex known in mammals, including humans. This reflex has been described for exposures to other inhaled nasal irritants. Interestingly, Peel et al. (Environ Health Perspect 2011) found robust associations of 8-hour maximum ambient ozone concentrations with bradycardia events among infants prescribed home cardiorespiratory monitors. This lends relevance to the cardiovascular toxicology found in the rat studies by Watkinson et al.

p.6-177, 6.3.3.2. Recent CV Toxicology Studies
line 17. The strain of mice should be specified.
6.3.3.2, p.6-177. It is not clear what CV effects of O3, besides mitochondrial DNA damage, were measured in the monkeys.

Table 6-39, p.6-182. The Perepu et al. study (2010) is a subchronic study and may be more appropriate in Chapter 7.

p. 6-184. The summary of the CV effects section is very well written. The suggested causative conclusion, however, appears somewhat conservative based on the results of the more recent studies. Most of the short-term exposure studies, though much more limited than those examining respiratory health effects, do demonstrate ozone-induced CV effects.

Comments on Chapter 7: Integrated Health Effects of Long-Term Ozone Exposure

General Comments:

In general, the overall format for this chapter is appropriate and the text is clearly written. The authors have thoroughly reviewed the recent literature and have included the most pertinent recent studies since 2006. There are some areas of redundancy with those in Chapter 6.

There are a few references to studies "In Press." These should be eliminated from the discussion.

Specific Comments:

7.1. Clear and concise introductory paragraph.

p.7-9, line 26. Should not include studies "In Press."

p.7-17, section 7.2.3(Pulmonary Structure and Function) needs a summary paragraph highlighting the relevance of the new findings from recent studies.

p.7-30. Last paragraph should also include findings from recent nonhuman primate studies that examine the structure/function effects of ozone on house dust mite-induced allergic airway disease (e.g., Plopper et al., 2007; Joad JP, 2008), or refer to these studies that are discussed later in the chapter (p.7-59).

p.7-30. A table of the recent toxicology studies would be helpful.

p.7-35. A brief summary of the major new findings and their relevance should conclude the section on Cardiovascular Toxicology.

p.7-36. line 12. "In Press" references should not be included.

p.7-37. Though the number of studies conducted in this area are more limited than those investigating respiratory effects, the data appears consistent that there is a causal relationship between long-term ozone exposure and CV effects.

p.7-61. Some of the exposure studies in the Laterality section, 7.4.9.1, are only for 6 days and are not long-term as defined by the authors (a month or greater). These studies could be included in Chapter 6.

p. 7-63, 7.4.9.3. The lengths of the exposures under Sleep Aberrations are not specified.

p. 7.67, 7.4.10.5. Recent study by Peel et al. (Environ Health Perspect 2011; see comment above) may have relevance to ozone and SIDS.

Dr. Daniel Jacob

Chapter 3 - Atmospheric Chemistry and Ambient Concentrations

Please comment on the adequacy of these and other changes to the chapter and recommend any revisions to improve the discussion of key information. In relation to ambient and background 03 concentrations, is material clearly, succinctly, and accurately provided? Where appropriate, please provide guidance that may refine the scientific interpretation and/or improve the representation of the science.

This chapter provides a very good overview of the atmospheric chemistry relevant to ozone pollution, the ability of models to describe it, and the ozone concentration patterns over the US. I have a number of suggestions for improving the chapter. The more important ones are given in bold. I would have liked to see some more discussion of long-term temporal trends, and comment more specifically on this below. I would have liked also to see some more discussion of the utility of satellite observations, in particular as top-down constraints on the emissions of ozone precursors. The discussion of background ozone is overall very good but I strongly recommend that supplemental section 3.9 be deleted because it is incorrect and misleading.

Specific comments (page, line):

(3-5, 23) Since off-road mobile sources are so important for NOx it would be useful to comment on what they represent. Agricultural vehicles, ATVs, lawn mowers, …?

(3-7, 37-38) Statement that coniferous forests are the largest source of biogenic VOCs is useless and misleading – deciduous forests are a larger source density of isoprene and this is what matters.

(3-11, 5) Do you mean peroxides rather than epoxides? Epoxides are exotic and low-yield.

(3-11, 8) hydroxycarbonyls do not come to mind as major products of alkane oxidation.

(3-12, 1-3) Isomerization of isoprene RO2s is very tentative and Crounse et al. find it to be unimportant. This whole business of isoprene chemistry and its effect on OH is very uncertain at present and I recommend that the ISA do nothing more than comment on the uncertain state of affairs.

(3-13, 27-30) repeats (3-13, 11-14).

(3-13, section 3.2.3) The discussion of heterogeneous chemistry effects on ozone elaborates on exotic mechanisms of unclear significance while missing two biggies: N2O5 hydrolysis and HO2 uptake. There has been a lot of recent literature on these two processes that have challenged previous literature and increased our knowledge. Some discussion would be in order.

(3-17) The discussion of NOx-limited vs. NOx-saturated regimes is confusing and sometimes seems wrong. The NOx-saturated regime is defined by dominance of NO2+OH as sink for HOx – it doesn't have anything to do with ozone titration. The NOx-limited regime is defined by dominance of peroxide formation as sink for HOx. Ozone production is dependent on "free radicals" (I presume that means

HOx, but is awkward because NOx are also radicals) in both regimes. There is no theoretical distinction between the low-NOx and very-low-NOx regimes, except maybe in the upper troposphere but that's irrelevant here.

(3-26, 9-18) I don't understand the point of this paragraph and suggest cutting.

(3-27, 9-12) It is not clear from the figure that the models are doing better in the mountain west than in the southeast.

(3-31, 13) "ozonesonde data" for what altitude?

(3-32, 8-10) the depletion of ozone at Trinidad Head under offshore flow conditions is due to deposition to land, not titration (Goldstein et al., JGR 2004)

(3-36) The text presents as given that wildfires have a large effect on ozone but in my opinion that is uncritical and flies against other evidence. Singh et al. (ACP 2010) found that California fire plumes are not enriched in ozone unless mixed with urban influence. Alvarado et al. (ACP 2011) found no significant ozone production in boreal forest fire plumes during ARCTAS. McKeen et al. found very little fire influence on surface ozone during ICARTT in summer 2004 even though there was a large influence on CO. In my opinion, there is little evidence that US wildfires make a significant contribution to domestic ozone. I understand that opinions may differ but at least the literature arguing against significant ozone from fires should be acknowledged.

(3-37, section 3.4.3) Some mention should be made in that section of the recent McDonald-Buller EST 2011 review article on the ozone background.

(3-38, 2) The GEOS-Chem model bias in the Southeast is for background conditions and is due to excessive ozone in clean air over the Gulf of Mexico, not error in US emissions, cf. Fiore et al. 2003.

(3-40, 5) The GEOS-Chem maximum over the SW in summer is not due to wildfires but to lightning and deep mixing, cf. Zhang et al. 2011.

(3-41, 20) Excessive vertical transport might also be a cause of excessive surface ozone over the subtropical Atlantic.

(3-44, 8-10) This paragraph seems gratuitous. Cut?

(3-47, 24-27) A 20-50 ppb bias would be of considerable concern! Could this be correct? It doesn't seem that it can be stated without discussion.

(3-103, section 3.6.3.1) I would have liked to see more discussion of long-term (multiyear) trends as these are so important for accountability of emission controls, background influences, and effects of climate change. There is a lot of literature on the topic besides EPA reports and Cooper et al. There is the Parrish et al. paper on increasing ozone in western US inflow, the Cohan et al. paper on the accountability of SIPs, the Leibensperger et al. paper on the effect of climate change over the past three decades. Trends have also been very non-uniform across the US, which is acknowledged in the text but I think that a map showing the geographical distribution of trends would be in order.

(3-109, 2) The flat profile appears to reflect the common observation for mountaintop sites due to orographical flow. I don't think that it is characteristic of rural sites. For example, a site like Harvard Forest has large diurnal variability in ozone due to deposition at night.

(3-103, section 3.6.4) This section overlaps with section 3.2.4 where the correlation of ozone with meteorological and chemical variables was much better discussed. I suggest cutting. The section is somewhat misleading, for example strong ozone-CO correlations are routinely observed in rural air in summer.

(3-114, 23) The statement about uncertainty in conversion of NOx to HNO3 and recycling is not helpful without some explanation of the processes involved. It's actually not clear to me what the authors have in mind. N2O5 hydrolysis? Isoprene chemistry?

(3-114, 24-25) The statement that most of the error in ozone modeling is from meteorology and emissions seems unsupported and is in my view misleading because it gets chemistry off the hook. I recommend cutting, here and in the body of the chapter.

(3-117, 3-8) I don't see the utility of saying that satellite instruments do not directly measure atmospheric composition. One could say that about other methods as well. "Stratospheric measurement of the total O3 column" doesn't make sense. I suggest that the authors put a more positive spin on the satellite measurements as these have demonstrated usefulness for ozone in the free troposphere and as top-down constraints on NOx, CO, and VOC emissions.

(3-119, 5) I don't see the point of "However"

(3-119, 8) this factor of two trend in global ozone is since pre-industrial times, not for the past decades. There's a good review paper by Oltmans on trends in background ozone over the past few decades.

(3-119,26-bottom) Again, I think that the section 3.6.4 is not helpful and could be deleted to advantage. That holds for this summary paragraph as well.

(3-125, section 3.9) I strongly recommend that this section be deleted. It used a faulty implementation of GEOS-Chem, with greatly excessive biogenic VOC emissions and ship emissions. The text suggests that the Harvard group stands behind the simulation but in fact it does not. The simulations were done by ICF and were supposed to replicate the Zhang et al. (2011) work, but in fact used a more recent version of GEOS-Chem and did so wrongly. The overall results are strange, beyond what I could attribute to the above errors. I am very familiar with the GEOS-Chem performance for PM, CO, NOx,etc. which is extensively documented in the literature (no citation to that work is given here). It doesn't look like what is described here. GEOS-Chem is a research model and should not be used without discernment by inexperienced users.

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

Please comment on the reorganization of this chapter and the adequacy, scientific soundness, and usefulness of the material presented and recommend any revisions to improve the discussion of key information.

Discussion of the importance of ozone as a climate gas is important in view of the need of concerted climate-AQ objectives in future regulations. Discussion of UV-B effects is also appropriate although these appear to be very small. The chapter acceptably delivers on these two topics but it has a number of minor errors. Also, I think that it needs to better inform on the climate effects of ozone precursor emissions, which in my opinion should be the most important item of this chapter because it directly relates to AQ regulation and is not obvious. There should also be some discussion of the new AR5 RFP scenarios as these will guide future climate-AQ studies. Itemized comments are listed below; important ones are in bold.

Itemized comments (page, line)

(10-3,1-26) That whole discussion is not well written and contains some inaccuracies. UV-B scattering does not depend on cloud droplet size distributions since the sizes are in any case much longer than the wavelength. Not clear to me why it would depend on altitude except in subtle ways. The troposphere is not opaque to outgoing IR radiation (atmospheric window). The text fails to mention the most important greenhouse gas (H2O).

(10-3, 27) A greenhouse gas is not defined by its interaction with solar radiation.

(10-3, 30 and 10-17, 25) Factor of 2 increase in tropospheric ozone seems higher than standard estimates, and the same paper is quoted on page 10-12 as reporting a 30-70% increase which is more mainstream.

(10-4, 4-10; 10-6, 1-5; 10-28, 1-6) The SRES scenarios are old history by now. I understand that the published work uses these scenarios but it behooves this report to discuss the new AR5 RFP scenarios, which are radically different in trends of AQ gases and in particular project no increases in the future except for the business-as-usual scenario. One cannot assume anymore that tropospheric ozone will increase in the future.

(10-5, 6) Again the text fails to mention H2O as the principal greenhouse gas.

(10-9, also section 10.3.3) The IPCC bar chart on radiative forcing referenced to emissions would be a very important addition to this report. It would greatly help in conveying the message on the very different sensitivities for the different emissions. Section 10.3.3 discusses older individual studies and gets mired into details (such as the effect of aircraft NOx) but fails to convey the consensus generated in the IPCC AR4 report including also the effects on aerosol forcing. The numbers in the report should be given here. In particular, an important conclusion of IPCC AR4 is that NOx emissions are climate-neutral within the range of uncertainty.

(10-10, 9) replace “climate” by “global surface temperature”? That would be more defensible.

(10-11, 7) A site in the San Bernardino Mountains is hardly relevant for the global trend in ozone.

(10-13, 6-8) I think that the important point in the Shindell et al. study is that the observed ozone trend since 1950 is much larger than predicted by models.

(10-13, 18-22) An important reason for the large shortwave forcing in the Arctic is the large SZA.

(10-14, 11) A more direct effect is the horizontal transport of heat, which cannot be regarded as a climate feedback.

(10-17, 6-7) Surface air at 30N is not NOx-saturated.

(10-27, 1) 10% for the contribution of the boundary layer to total tropospheric ozone seems low for polluted regions.

(10-28, 12-13) I don't see the point (also in the text) of citing the older Naik work that "a carefully combined reduction of CO, VOCs and NOx emissions could lead to net cooling". Having such a "carefully combined reduction" is wishful thinking, both in terms of practical policy and scientific uncertainty.

(10-28, 23) The cooling effects of CH4 controls would in fact be realized immediately.

Dr. Steven Kleeberger

Chapter 8 - Populations Potentially at Increased Risk for Ozone-Related Health Effects

The introduction to Chapter 8 has been revised with expanded discussion to better capture the intricacies associated with characterizing populations potentially at greater risk for O_3-related health effects, utilizing the terms identified by the CASAC panel (i.e. intrinsic, extrinsic, increased dose, greater exposure).

Please comment on the adequacy of these revisions to clarify the consideration of potential at-risk populations, and recommend any revisions to improve the characterization of key findings and scientific conclusions.

Adequacy of the revisions to clarify the consideration of potential at-risk populations:

Chapter 8 is much improved after revision of the initial draft. The revised chapter has attempted to clarify the terms 'susceptibility' and 'vulnerability' as they pertain to increased risk of detrimental effects following acute or chronic exposures to ozone. As suggested by the CASAC review members, the authors categorized risk of detrimental effects into intrinsic, extrinsic, and increased dose factors. This artificial categorization provides a framework for discussion of the risk factors. The authors also indicate that some of the factors that are included in the three categories are often connected and/or not easily separable for discussion (page 8-2). The categorization is somewhat unwieldy but it does attempt to clarify the difference between susceptibility and vulnerability.

As suggested by the first review, the authors have been more inclusive of animal toxicology literature where the studies support human studies or where human studies have not been performed but biological plausibility suggests importance. This addition enhances the value of the document.

A table that summarized findings of genetic investigations was recommended in the first critique, but was not included in the revised chapter 8. A table should be included.

The summary of Chapter 8 is not particularly useful. While some of the major points are summarized in the text, there was not a comprehensive synthesis of the findings for the reader to consider. This would seem to be especially important for regulatory purposes. A table that summarizes the risk factors and the strength of evidence for their importance in human and animal studies is recommended (see table 6-65, page 6-233 for example).

Other comments:

Page 8-1, line 3; page 8-5, line 23; page 8-6, lines 1 and 17; page 8-8, line 8. Remove 'both'

Page 8-2, line 10. Change sentence to …this chapter is to identify and understand the characteristics…

Page 8-2, line 16. It is not clear what 'different role' means.

Page 8-11, line 11. 'Sycalmptomatic' should be 'Symptomatic'?

Page 8-11, line 22. Change sentence to …epidemiologic studies have examined…

Page 8-18, beginning of section 8.4. While the study by Triche et al is an example of the potential role for genetics in ozone-related health effects, other studies could be cited that provide a better segue to the section including inter-individual (human) and inter-strain (rodents) variation in responses to ozone in otherwise healthy individuals.

Page 8-19, line 7. Change sentence to …low frequency minor alleles and therefore…

Page 8-19, line 19. 'polymorphism' should be plural.

Page 8-19, line 20. 'response' should be plural.

Page 8-20, lines 18-20. The point should be made here that one of the reasons for the inconsistencies could be that different genes may be important for different phenotypes. This point has certainly been demonstrated in rodent studies, and should be included in this section.

Dr. Frederick J. Miller

Chapter 5: Dosimetry and Mode of Action

General Comments

The 2nd draft of this chapter has been greatly improved by the addition of material on gas transport principles, the importance of mode of breathing, expansion of the importance of physical activity in determining dose, and the organization of the discussion on the role of the ELF to name just a few areas. The mode of action material has been strengthened by the addition of results from animal studies.

While the chapter is longer than the 1st draft was, it provides a clearer picture of the role of dosimetry in integrating animal and human data for evaluating the potential for O_3 to cause various effects in humans following acute and chronic exposure to this pollutant. The text now does a good job of showing how mathematical dosimetry model results agree with experimental dosimetry results from studies in human subjects.

There is still a need to do a better job of treating species homology and extrapolation of animal data to humans. Also, the authors need to better link some discussions in Chapter 5 to other Chapters and Sections. For example, Section 5.3.7 on Airway Remodeling contains an inadequate discussion of the ability of O_3 to remodel the lower respiratory tract of monkeys as it only discusses changes occurring in adult animals, while ignoring all of the work done by the UC Davis group on infant monkeys. At a minimum, the reader should be referred to Section 7.2.3.1, but more importantly, the reader misses the impact of the implication of these results for children living in areas of higher O_3 levels.

Some of the material that was in the Mode of Action sections in the 1st draft has been moved to Section 5.5.2 on Homology of Response. An example is the discussion of the Dormans et al. (1999) study. However, since the authors have still failed to address a criticism this reviewer raised about this study and other such studies, the comment is repeated here:

> "…the authors need to be careful about making statements that a study shows one species is more sensitive to O_3 than another. A good example of this can be found on page 5-34 starting at line 20. The text states that Dormans et al. (1999) exposed rats, mice, and guinea pigs to O_3 and found guinea pigs to be the most sensitive with respect to alveolar macrophage elicitation and pulmonary cell density in the centriacinar region. And mice were most sensitive to bronchiolar epithelial hypertrophy … and the list goes on. Such statements about sensitivity are simply not valid unless there is normalization to the dose received. One species may remove more O_3 than another in the nasopharyngeal region or one species may receive a greater pulmonary dose."

Concerning the thickness of the ELF in the alveolar region, the authors present the results of Bastacky and colleague (1995) from the laboratory of John Clements for measurements of the thickness of the surfactant layer. Dr. Clements has long been interested in the thickness of the surfactant layer. While they report a "mean" surfactant thickness over "flat alveolar surfaces" of 140 nm, they state that it varies from a few nm to as much as about 900 nm at alveolar wall junctions. They report that 4 % of the surface area has a thickness below their limit of detection, which was 2 nm. In addition the median thickness was 100 nm, which means that a significant percentage of the surfactant layer is only a few nm

thick. Even if only 10% of the alveolar surface has a few nm surfactant layer, this could have a large impact on epithelial injury caused by O_3 and could explain the patchy network of damage that has been observed in animals following O_3 exposure. Thus, it is not appropriate to ascribe all alveolar region changes as being due to ELF reaction products or a cascade of these products; therefore, the text on page 5-18 lines 23 – 25, while a reasonable statement, should be reworded to make it clearer that both direct reaction of O_3 with alveolar cells and surfactant layer O_3 reaction products reacting with alveolar cells is occurring. This clarification needs to be carried forward to the chapter summary as well as to the integrative chapter.

Specific Comments

Page, line	Comment
	There are numerous instances in this chapter where the authors use the word "which" when they should use "that". A Technical Editor should go through the document for grammatical errors.
5-5, 33	There is a confusion imparted by stating that "uptake efficiency" is that same thing as "fractional absorption". They are not the same, and this leads to confusion in Table 5-1 where F_{URT} and F_{LRT} sum to a value > 1. Efficiency refers to the fraction taken up in a region as a function of the total amount of material entering the given region, while fractional absorption is based upon the amount inhaled and represents normalization by region such that their sum cannot exceed 1.
5-7, 23 - 35	This paragraph is confusing because the wording on the 3rd line from the end makes it sound like the model predictions do not agree with the experimental results. However, that is not the case; moreover, the model predictions were made many years before the experimental studies were conducted. Some rewording of this paragraph is in order.
5-8, 4	The text here is an incorrect statement of how Miller et al. (1985) modeled the LRT uptake of O_3. Reactions with the alveolar region ELF (i.e., the surfactant layer) were not excluded – rather the concentration of molecules that can react with O_3 is exceeding small compared to those that are contained in the ELF of the URT and TB regions.
5-8, 12	The text here makes a very important point that should go forward to the summary for this chapter and to the Executive Summary chapter. The variability in path length from the trachea imparts a significant variability in localized acinar dose. Thus, the authors are right on target when they state "This could have implications in regional damage to the LRT, such that even though the average LRT dose may be at a level that would be considered insignificant, local regions of the RT may receive significantly higher than average doses and therefore be at greater risk of effects."
5-8, 19	The authors did not address the point I raised in the 1st draft about the Wiester et al. (1987) paper. The comment is repeated here: "The discussion here does not include Wiester et al. (1987) where only 40% in the total respiratory tract was measured over a concentration range

	from 0.3 to 1 ppm O_3. Has this study been discredited? If not, then it should be included to reflect that there is not complete agreement in the published literature about how much O_3 is removed in the head in animals." This will also require that the paragraph be rewritten to reflect a wider range of O_3 uptake is seen from experimental studies.
5-9, 1st full paragraph	The thrust of the results presented in this paragraph is simply a repeat of the findings of Aharonson, who showed that as flow rate increases the localized flux into the tissue increases but the overall uptake decreases due to the shorter residence time of the inhaled air in the given region.
5-9, 34	The authors state that because the O_3 dosimetry model predicts low tissue dose in the trachea, but injury is seen there, that net dose may be a better predictor of local toxic tissue dose. If this were indeed the case, then much more significant effects in the TB region should be seen because the net tissue doses in the trachea and upper portions of the TB region are practically the same as the net dose in the alveolar region.
5-13, 12	The authors state that the difference between nasal and oral uptake is not large and so the difference is probably not biologically significant. However, the most reliable study of those listed in Table 5-1 to address the point of nasal versus oral breathing differences in O_3 uptake is, in the opinion of this reviewer, the study by Nodelman and Ultman (19999). With shallow breathing, these authors showed a reduction from 0.9 to 0.8 for nasal vs. oral breathing. At a flow rate corresponding to moderate to heavy exercise, nasal uptake was 0.4 while oral uptake was 0.25, which is a highly significant difference. Moreover, the reduction in scrubbing efficiency with oral breathing means more O_3 is delivered to the deep lung where the epithelial cells are more sensitive to O_3 exposure. Thus, the text should be modified.
5-13, 15	Shouldn't "of the RT" be "on the RT"?
5-32, 20	This is almost a verbatim restatement of text that appears on the previous page.
5-33, 1-14	Most of the studies discussed here were with very high O_3 exposures and are not likely relevant to human exposure – suggest deleting this paragraph.
5-33, 19	UA as an abbreviation for Uric Acid is not contained in the glossary.
5-35, 26	TLR4 is used both capitalized and not capitalized here and on subsequent pages. Be consistent.
5-38, 26	Instead of "an older study", the authors might consider using "an earlier study".
5-40	The introductory paragraph to Section 5.3.6 is excellent.
5-45, 32	This paragraph should be deleted. The text provides weak evidence at best from in vitro studies and is mostly conjecture.
5-50, 29	The definitive study for understanding the variability in inter-subject changes in FEV1 response to O_3 has not been done because the studies have not controlled for the conducting airway volume, which is likely the driver as modeled by Overton et al. (1996). The authors correctly

	cite this concern, but the text here should contain a caveat that arises from the results of Overton et al. (1996). By controlling for the conducting airway volume, one would be able to see how much of the inter-subject variation in FEV1 response at a given O_3 exposure level is actually just that.
5-57	Section 5.4.2.2 on Pre-existing Diseases and Conditions is very well written. And the text on page 5-58 from line 9 – 12 should go forward to the chapter summary and the Executive Summary.
5-65	The Attenuation of Responses section is difficult to follow because there is a mixture of endpoints that show attenuation and those that do not. The authors might consider a short introductory paragraph where the endpoints that are attenuated with O_3 exposure are listed followed by a listing of those that are not. Then the paragraph could end with a sentence that now these various endpoints will be discussed. In addition, the bottom line does not come through for this section about how attenuation is essentially a "false negative" because other endpoints continue to worsen with more O_3 exposure. Moreover, the animal studies show that various lesions continue to worsen even though endpoints like pulmonary function are attenuated.
5-68	In the introductory paragraph to Section 5.5, the authors state "This will not be a quantitative extrapolation of doses where O_3 effects have been observed". The authors could easily provide an example of how quantitative extrapolation can be done by expanding Figure 5-11 to include a Panel c that is based on Figure 9-6 of Miller et al. (1988). That figure contains data on lavage fluid protein (LFP) levels in rats, guinea pigs, and rabbits as a function of model predicted tissue dose of ozone that has been normalized to take into account differences among the species in body weight and LRT absorption. Moreover, the data from the human studies for this endpoint could be added to Panel c to provide a clear example of how quantitative extrapolation can be done. The importance of such an exercise is not to extrapolate LFP per se. Rather it would illustrate the importance of the animal results underpinning implication for humans. It would also help dispel any "So What" attempt to dismiss the acute changes seen in human studies as being not of concern by laying the groundwork of the importance of effects seen in chronic exposure studies in animals with the knowledge that similar acute effects can be demonstrated in both animals and humans.
5-73, 10	The statement here about animals at rest underestimating risk to humans with exercise is an apple to orange comparison. One needs to normalize to the dose received by each species and convert concentration-response data to dose-response data before such statements should be made.

Dr. Howard Neufeld

Comments on Chapter 9 – ISA for Ozone and Other Photochemical Oxidants

This is a well-written summary of the current state of knowledge concerning the impacts of O_3 on plants and ecosystems. I thought the organization from leaf to ecosystem was excellent, and the discussions were of an appropriate length and depth. I agree with the majority of the conclusions regarding the degree of causality with exposure to O_3. The authors have successfully incorporated most, if not all, of the criticisms of the earlier document and ended up with a very readable and comprehensive account of the impacts of ozone on plants and ecosystems. Most of my comments are minor in nature. At the end, I list those typos that I found.

On page 9-3, the authors state that there have been no methodological advancements since 2006 that have fundamentally altered our understanding of O_3 effects on plants and ecosystems. I think this is too strong a statement. Although it is true that no new "breakthrough" technologies may have been developed in that period, new understanding did arise from using existing technologies in new ways. For example, researchers used the Li-6400 gas exchange system to look intensively at dynamic stomatal responses to O_3, and out of that came the concept of stomatal sluggishness. One researcher (Grulke) did develop a new system that can measure photosynthesis and stomatal conductance while simultaneously applying an O_3 treatment to the leaves. And at the molecular level, advancements in the analysis of arrays have allowed researchers to study how O_3 affects gene upregulation and downregulation. Thus, I would temper this sentence by saying that there were *some* methodological advances.

I was particularly pleased with the review of past literature and the statements confirming that much of the older results are still relevant. I was also happy with the synthesis of the various exposure methodologies and the clear statements and analyses showing the veracity of the results from these earlier technologies. For many years now, the data obtained from either CSTRs (continuously stirred tank reactors) or OTCs (open-top chambers) have been questioned, but these new analyses clearly show that the results obtained from these studies continue to have relevance and are highly correlated with the results obtained from FACE systems. In other words, there is a lot of internal consistency among the various exposure methodologies. This part was very well done.

In Section 9.2.4, which discusses various FACE-type systems, the authors for some reason left out the Finnish FACE system, even though that system is discussed later in this same chapter. I would suggest including a mention of it here (pg 9-6). The same criticism applies with regard to the Kranzberg Forest Exposure system, which is a variant on the more traditional FACE systems.

Bennett and others (2006, Env. Poll., 142:354-366) utilized a gradient in exposure along Indiana Dunes National Park to assess O_3 injury on plants, and I would suggest including that study in addition to the San Bernardino study. Bennett and others clearly showed how pollution from Chicago was affecting plants downwind across Lake Michigan, which is where Indiana Dunes National Park is. The study by Winner et al in Shenandoah National Park, while showing an elevational gradient in injury in plants, should have the conclusions tempered by the fact that there were probably other confounding gradients involved also, such as higher N deposition and rainfall at higher elevations.

In the discussion comparing results in OTCs and FACE and gradient studies, the authors mention the possibility of chamber effects using OTCs. In many studies, there were indeed chamber effects, but few to no interactions between ozone exposures and chamber, suggesting that using the OTCs for determining relative effects is okay. In studies I did in the Smokies, we directly compared plants in 1X ambient chambers with those growing in non-chambered plots. For most parameters measured, there were no significant chamber effects. See Neufeld et al. (1995, New Phytologist 130:447-459) where there were no chamber effects on black cherry seedlings except for height growth; see also Neufeld et al. (2000, Env. Poll. 108:141-151) where there were no chamber effects for any parameters measured on several conifer species. Perhaps these studies could be included to help show why OTCs are still useful for assessing O_3 impacts on plants.

On page 9-10, the authors simply state that Gregg et al. found "similar" effects as the previous study cited. Given the large magnitude of effects in the Gregg study, I think it prudent to perhaps elaborate just a bit here on the Gregg study to put it into a better context. I know that the authors devoted a separate section later on to Gregg's study, but this one sentence here seems too brief for such a significant piece of work.

On page 9-21 the authors are discussing various proteomic and transcriptomic studies. These topics are well done, and the authors do a nice job of distilling the major patterns that are apparent, even after just a small number of studies have been published. However, perhaps the Biswas et al. (2008) paper (see citations) on wheat genotypes and breeding should be mentioned in either this section (which is discussing genes at the molecular level) or in a later section (i.e., 9.4.4.1, pg 9-61).

On page 9-38 the authors review the causes of decline in photosynthesis due to O_3. One possibility that has not been extensively discussed is whether or not photosynthesis and other physiological processes proceed at near normal rates in those parts of the leaf that do not show O_3-induced stipple: that is, are the green areas that remain uninjured still photosynthetically competent? Most studies of gas exchange simply express rates on a total leaf area basis, without regard for how much of the leaf is showing stipple or injury. When leaves subject to acidic deposition were measured for their gas exchange (Neufeld et al. 1985), the rates were unaffected if expressed on a green leaf area basis, whereas if the necrotic areas were included, this necessarily lowered the rates. If rates are high in visibly unaffected portions of the leaf, then that suggests several things: (1) that effects of O_3 are highly localized within the leaf; (2) that portions of the leaf that are uninjured continue to function at near normal rates, and (3) that declines in photosynthesis due to O_3 may not always result from a general inactivation or destruction of all RUBISCO and associated enzymes, but may simply be due to loss of competent leaf area in those areas exhibiting stipple.

In section 9.4.2, I think the authors could have beefed up their discussion of genetic variation in non-crop species. For example, Somers et al. (1998) and others (Chappelka et al. 2003, Souza et al. 2006) showed extensive genetic variation in symptom expression in the field for both herbaceous and woody plants. Furthermore, this section might benefit from a slight extension of the discussion of the value of genetic diversity among wild plants.

The meta-analyses of Wittig et al. (2009) which purport to show 7% reductions in growth at O_3 as low as 40 ppb are perhaps worthy of further discussion. Although the magnitude of reduction is consistent with previous studies, as pointed out by the authors of this chapter, they are expressed relative to growth in charcoal-filtered controls. There is current discussion as to whether or not a charcoal-filtered control

is appropriate if background O_3 is near 40 ppb. Furthermore, none of my tree studies in the Smokies showed any detectable growth reductions in OTCs below ambient levels of O_3. Therefore, I think these conclusions may warrant some rethinking and further analysis.

I was glad to see the discussion of the potential impacts of ozone on lower plants, such as mosses and lichens. These plants cover a substantial portion of the surface of the earth, and while small in stature, have large ecological footprints. If they turn out to be affected by O_3, it could have ramifications for ecosystems around the world.

On page 9-46, the authors refer to the trees in the AspenFACE site as a "forest in Wisconsin". I think this is somewhat misleading. Every one of those trees was planted, so even though it could be considered a forest, it is a highly artificial one. I would augment this by referring to this forest as an "artificial forest", or a "planted forest". And even if it is considered a "forest", it is limited to just three species, or in the other half of the plots, to one species with many genotypes. Neither is typical of a natural forest.

In section 9.4.3.2, Summary, last paragraph, the authors might consider modifying or adding to the conclusionary sentence. I think it is important to stress that many O_3 effects on native vegetation in the field were found at ambient levels of ozone, to distinguish those effects found using elevated O_3 under controlled conditions. It's important to show and explicitly mention that current ambient levels of O_3 are negatively impacting vegetation.

On page 9-54, there is no mention of David Weinstein's analysis of the potential impacts of O_3 on trees in Great Smoky Mountains National Park. This analysis was published in a SAMAB report. I think it is important to include this and to expand the discussion beyond California.

I am surprised that most of the current modeling for O_3 effects on plants is using data that is 20 to 25 years old (see pg 9-56, bottom). Also, these models are all using data obtained from just one research group. Are there no other more current or varied data sets to use to parameterize these models? I find that incredible and somewhat disappointing as it perhaps indicates how the lack of funding has hindered our attempts to learn more about the effects of O_3 on plants.

I was also surprised not to see any papers by Muntifering when discussing the impacts of O_3 on the nutritive quality of crop and range plants. His research group, in conjunction with European researchers, has shown declines in the quality of forage after exposure to ozone (section 9.4.4.2, pg 9-64).

Figure 9.7, pg. 9-69, could possibly be modified to also include a *decrease* in water loss due to the loss of canopy leaf area resulting from O_3 exposure. A loss of canopy would also open up more of the soil surface to direct radiation input, which might enhance evaporation from the soil surface, unless there are feedback loops where vegetation in the lower soil layers becomes denser and shades the soil surface.

When discussing sluggish stomata, the authors should consider that in some cases, stomatal conductance is reduced when stomata begin exhibiting sluggish responses. So, if they fail to respond to environmental stimuli, and remain open, but not to the same degree as in the absence of O_3 exposure, then there may not be *enhanced* water loss relative to a no O_3 condition. It could, in fact, be less.

In section 9.4.9.2, the authors state that after a single 4 hour exposure to O_3 there was reduced pulmonary macrophage phagocytosis in a toad. It would help to specify the actual exposure in ppm*hrs.

I was pleased with the sections dealing with the various exposure indices, and the development of exposure-response functions. The analyses were carefully done and results clearly show detrimental effects of O_3 on the growth of plants, and in particular, the important role for higher O_3 concentrations. The separate discussion of the results from Gregg et al. (2003, Nature) which show an 82% reduction in biomass, presumably due to O_3, compared to less than 20% for other tree species in the same genera in other studies, points out how unusual Gregg's results were. The authors adopt the most parsimonious explanation, which is that these are valid results with no confounding effects. While this is the most logical conclusion to reach at this time, it would seem prudent to wait until someone replicates this experiment before placing too much emphasis on the results.

In conclusion, the chapter is well written, comprehensive, and brings together most of the relevant literature published since the 2006 report.

Typos
Pg and lines
9-12, line 22 – the superoxide chemical structure is missing a minus sign
p-14, line 6 – subscript needed in CO2
9-16, figure 9.4 legend – in section (a), change "reactions" to "reaction and "is" to "are"
9-18 – Arabidopsis is sometimes italicized, and sometimes not. Decide whether to italicize, and then do throughout document.
9-18, line 12 – change MAP kinase to MAPK
9-21, line 14 – insert space before "ethylene"
9-25, line 5, there is an extra period at the end of the line; line 12 – change "was" to "were"
9-28, line 22 – insert "ozone" before "for 60 days…"
Line 37 – insert "ozone" before "conditions"
9-37, line 3 – take out "in" before "have been…"
9-46, line 9 – subscript 3 in "O3"; line 16 – Change "Wittig et al" to "They"; last line – take out "the"
9-47, lines 18-20: rewrite as: "…; however, apparent direct O_3 treatment effects were obscured by high variability in the data."
9-49, line 13 – change "meta-analysis" to plural; change "demonstrates" to "demonstrate"
Line 17 – refer to the forest as a "planted" forest, since it is not natural.
Lines 26-27 – should this conclusion refer specifically to "ambient" O_3?
9-51, Table 9-1 – the first species name is misspelled. Should be "*Apocynum*" with an "m" at end
9-53, Table 9-3 – for Tregro section on carbon uptake, insert "of" at beginning of last line
In TEM section, carbon uptake section, change "vegetations" to singular
9-56, line 23 – take out comma after "damage"

9-57, line 6 – change "provided" to "provide". In fact, rewrite entire paragraph in present tense.
Line 15 – insert "the" before "Mid-"; line 19 – change "those" to "these"; line 23 – change "sink" to plural;
9-58, Table 9-3 – use negative exponents in units at bottom of table in line a.
9-59, line 10 – need a space after AQCD
9-61, line 3 – change "phenolics" to singular; line 34 – change "merits" to singular

9-64, line 20 – take out "was" and add "of" at end of line; line 22 – take out "were" and rewrite as: "…considered by these authors.; line 24 – change "demonstrates" to "demonstrated"; line 27 – change "is" to "was"; line 29 – take out period before citation.
9-69, line 3 – insert "widths" after "aperture"
9-70, line 28 – take out "of"
9-74, line 30 – sentence is missing some words. Needs to be fixed.
9-76, line 5 – change "have" to "had"; line 25 – italicize *Quercus ilex*
9-79, line 13 – insert "an" before O3-tolerant; line 26 – change "decreased" to "decrease"; line 31 – change "suggested" to "suggest"; line 32 – change "were" to "are"
9-82, line 25 – insert "the" before "exotic"
9-83, line 34 – change "the" to "that"
9-84, line 4 – insert "showed that" after "community"; line 5 – italics for scientific name; line 6 – take out "most studied" and italicize scientific name again;
9-85, line 26 – insert "the" at end of line; lines 28, 29 – italics for scientific names
9-86, line 12 – insert "the" before "Carpathian"
9-93, line 9 – change "to" to "in" before "plants"
9-94, line 18 – take out comma after "site"; line 20 – take out parentheses around scientific name; line 31 – spell out genus name for Japanese beetle.
9-95, line 11 – change ";" to a comma.
9-97, line 6 – change "were" to "was"; line 7 – insert "litter from" before "trees grown"; line 12 – move scientific name up to line 10 where earthworms are first mentioned; line 30 –change "is" to "are"
9-99, line 18 – take out comma after scientific name
9-100, line 8 – change "that" to "than"
9-101, line 2 – insert "the" before "secondary"; line 12, insert comma before "temperature"
9-102, line 3 – definition of SUM06 is incorrect. It should be "…concentrations at or above 0.060 ppm. Add a comma after "summed". Line 6 – insert "the" before "summed".
9-110, line 7 – change "occurred" to "occur" and "were" to "are"; line 8 – change "were" to "are"
9-111, line 32 – "stomata" should be "stomatal"
9-114, line 25 – insert "the" before "secondary"
9-141, line 10 – add "with" at end of line

Comments on Chapter 10 – ISA for Ozone and Other Photochemical Oxidants

This short chapter is, like the previous one, well written. It clearly summarizes a wide variety of articles on the impacts of tropospheric O_3 on possible climate change and does so in a very readable format. Most importantly, it succinctly summarizes the various states of knowledge concerning tropospheric O_3 impacts on climate change.

I found very little of substance to comment on. Most sections were well done and reached logical conclusions based on the literature and data available. In section 10.3.2.1, pg 10-11, there are no referrals to the EPA Trends reports, which I found puzzling. This section would benefit by their inclusion.

In Section 10.4.4, there are no mentions of Joe Sullivan's, Alan Teramura's or Martin Caldwell's work on effects of enhanced UV-B on plants. Perhaps this is because most of this work was carried out prior to 2006, but even so, if this section is briefly reviewing UV-B effects, their work would be highly relevant here.

On pg 10-6, the authors use the word “deposited” when discussing albedo effects. Albedo doesn’t affect the amount of energy deposited to a surface, only the amount that is retained at the surface. Thus, perhaps the authors would consider replacing “deposited” with “retained”, since that more clearly reflects the mechanism of action here. On page 10-24, it seems to me that the last two sentences of the aquatic ecosystems section would better fit in the next section on changes in biogeochemical cycles.

The rest of the chapter is very well done, and I have no major comments.

Typos:
10-7, line 2 – I think this statement is too strong. I would insert “some of” before “these processes” and on the next line, replace “is” with “can be”; line 7 – change “are” to “is”;
10-13, line 17 – I would again replace “deposited” with “retained”
10-15, line 29 – change “leading” to “lead”
10-16, line 26 – change “at” to “by” before “2030”; line 27 – insert “may” after “precursors” and change “increases” to “increase”
10-25 – insert “the” before “southeastern”

Dr. Armistead (Ted) Russell

While improved, there are a number of issues, some lingering from before.

Chapter 3:

1. From before: Please provide more quantitative relationships between the various metrics (e.g., 1-hr max, 8-hr max and 24 hr avg). This is important to better interpreting the health results. I would like to see quantitative relationships between the metrics on a city-by-city basis, if possible, showing the range of relationships (i.e., slopes, intercepts).
2. From before: Please provide an objective approach to deal with uncertainty and bias in the model (or whatever approach you recommend for use) estimates of background. This is a science issue.
3. New: Given the variety of new studies of how to estimate "background" ozone, a more thorough assessment of the methods (particularly those using finer scale modeling) should be given. What is the recommended choice and why?
4. The figures and other analyses should focus on the likely form of the standard, e.g., 4^{th} highest 8-hr average (or the three year average of 4^{th} highest), not showing other metrics except to make a point (which is really not done currently).
5. Provide more information on temporal trends, but not just of the higher end of the distributions. I would like to see the mean, and some information on the distribution, over the last 20 years, possibly showing the frequency distribution of concentrations for a specified, consistent, set of sites.
    a. Along those lines, it would be good to also provide more information on what is happening in the 60-70 ppb region over time given that this is the likely range of a suggested revision to the standard.
6. Fig. 3-58b looks wrong (the area under the red curve looks smaller).
7. Section 3.9 is weak. Further, this section suggests a number of issues are important: What does important really mean in this context? (The word "important" is used elsewhere, but it is hard to interpret how important it is given how often the word is used.)
8. It would be good to look at how the information from this chapter will be used in the REA and PA and then make scientific recommendations on the inputs to those approaches. In particular, the rollback model will require a number of coefficients that are informed by the analysis of the temporal trends (and how the distributions are responding to controls) and the estimated "background". Further, BenMAP and APEX will use some sort of modeling results (or a fusion of data and various models). The ISA should provide specific recommendations as to the inputs to that modeling. In essence, work the process backwards starting with what type of analyses are needed for the PA and REA, and then provide recommendations and information needed to best support those analyses. As noted above, how to treat biases in the "background" ozone modeling should be spelled out with specific recommendations made.

Chapter 10:

9. The increased brevity is appreciated, though there are still sections that seem to ramble without getting to the point (particularly 10.4.5).

10. In regards to the UV-B related effects , the health effects are suggested to be "small". What is "small"? Be quantitative as much as possible. This part of the ISA actually sounds to be evasive (maybe that is tied to being rambling).
11. The conclusion is made that the effects" cannot yet be critically assessed within reasonable uncertainty." What part(s) of the process are most uncertain, and which uncertainties are the critical roadblocks.
12. On page 10-28, it is stated that "Reduction of tropospheric ozone concentrations could therefore provide an important means to slow climate change…" However, the Executive Summary and Chapter 2 conclude that the relationship is "likely causal." The statement in this chapter sounds more like "causal".

Executive Summary/Chapter 2:

1. The Executive Summary and Chapter 2 both are much more specific than Chapter 10 about relationships between ozone and outcomes, as, the Exec. Summary and Chapter 2 have bolded sentences with conclusions about the level of relationship (e.g., "causal", likely to be causal"…), similar to what is done in the health effects-related chapters (Chapters 6&7). Such statements (similarly bolded) should be made in chapter 10, with the evidence used to make that determination. As part of this, explain how changing radiative forcing is only "likely" to impact climate change (i.e., why changes in tropospheric ozone levels are causal in impacting radiative forcing, but only likely to be causal in impacting climate). The current statements in the chapter appear to support a "causal" determination, so the text and the linkage strength need to be made consistent.

Chapter 9:

1. I think the current Section 9.6.4 is actually the chapter Summary, and should be Section 9.7. This section should also contain a summary table of causal determinations (similar to Chapters 6 and 7).

Dr. Helen Suh

Charge for Chapter 4 - Exposure to Ambient Ozone

Revisions made to Chapter 4 in response to CASAC comments include clarifying the discussion of the relevance of central-site monitoring data for epidemiologic studies, together with potential bias and uncertainty due to exposure error; revising the summary section to be more concise and focused on the main points of the chapter; and preparing tables to summarize field study data and facilitate comparison of exposure models. In addition, material has been added discussing averting behavior on high-03 concentration days.

Please comment on the adequacy of these and other changes in responding to the Panel's comments. Please provide comment on revisions that may further improve the utility of discussion for characterizing personal-ambient exposure relationships and for interpretation of epidemiologic results in subsequent chapters.

General Comments

The revised chapter is a substantial improvement over the previous version. The chapter is a comprehensive, clear, and thoughtful presentation of what is known about ozone exposures and factors that affect exposures. Further, the Chapter does a good job of discussing what research is new since the last review.

The findings discussed in the Chapter have substantial import and implications for other ISA chapters, especially Chapters 2, 6, 7, and 8, as results can be used to help interpret findings from health studies; however, findings from Chapter 4 are not well integrated into the rest of the document. Results from Chapter 4 should be brought forward into discussions of exposure error and confounding in Chapters 6 and 7 and of increased risk in Chapter 8. Correspondingly, Chapter 4 can be improved in several places by integrating results on concentrations and modeling from Chapter 3 (as noted below for the population proximity to monitors discussions). In so doing, Chapter 4 discussions would be placed in a broader context and tied to actual data. Further, Chapter 2 would be improved substantially by being a synthesis of results across the concentration-to-health continuum.

Chapter 4 emphasizes short-term exposures (of one day or less), with little discussion of long-term ozone exposures. Although this emphasis is understandable given that exposure studies have focused on short-term exposures, it is important to expand the section to include discussions of long-term ozone exposures within each section, especially given the observed associations between long-term ozone exposures and mortality. Similarly, the discussion would benefit from greater focus on findings of personal-ambient relations when ambient ozone concentrations are near or lower than the current standard. In addition, some sections, such as the sections on exposure models and exposure error, would benefit from more references. Finally, it seems that the section presenting results showing results from the APEX-O3 that show impacts on personal exposures from just meeting various design values (or ambient O3 concentrations) does not belong in the ISA or should be better justified. This section is more fitting to the Risk and Exposure Assessment.

Specific Comments

Section 4.1

- Page 4-1, line 7: The use of the word "definitive" when referring to existing relevant information from the 2006 O3 AQD is not appropriate. Perhaps "unchanged" or "is still relevant".

Section 4.2

- Page 4-2, line 24-25: I would omit the sentence beginning "F_{inf} is a function of …characteristics." As noted in the next sentence, F_{inf} is a function of several factors in addition to building air exchange rates.
- Page 4-3, line 6: The list of factors contributing to spatial variability should include topography.

Section 4.3

- This section could be expanded to examine personal-ambient associations for weekly, monthly, or seasonal averages, if personal and ambient ozone data from some of the referenced studies could be obtained.
- Page 4-8, line 16: replace "trend" with "levels" or "concentrations".
- Page 4-8, lines 26-34: The impact of exposure averaging periods on the personal-ambient relationship should be discussed, especially given the importance of longer averaging windows to epidemiological studies.

Section 4.4

- Page 4-19, lines 1-15: This paragraph seems misplaced and not needed, as it does not contain any results. It would be better to include results from CHAD that have been reported in a peer-reviewed journal.
- Section 4.4.3: The analysis of proximity is of unclear significance, particularly given the earlier statements. If there is substantial spatial variability introduced by roadways, which exhibit significant variability over small spatial scales, it is likely that proximity would be a poor predictor of a monitor's representativeness. For this section to be useful, data showing how ozone concentrations varies around monitor locations would be helpful. In absence of data, modeling results shown in Chapter 3 could be used to demonstrate whether proximity to monitors matters for population exposures.

Section 4.5

- Page 4-27, lines 13-25: The accuracy and precision of the model should be reported.
- Page 4-27, lines 26-34: The difficulty of using geostatistical and chemistry-transport models to estimate exposures also pertains to all of the outdoor surface models discussed in this section. This paragraph should be expanded to include all of the outdoor concentration models or should be reworked.
- Page 4-32, lines 1-15: This section seems inconsistent with the rest of the exposure chapter, with its discussion of research needs and models under development but not yet published. The discussion

of research needs could be reworked to discuss sources of model uncertainty. The discussion of models under development should be deleted, given the ISA's emphasis on peer-reviewed studies should be deleted.

Section 4.6

- Much of the discussion in this section is geared toward the impacts of short-term (e.g., ≤24h) exposures. The section would benefit from discussions of the effect of spatial and temporal variability in longer term exposures, for example of one month and on year, especially given the importance of chronic ozone impacts on mortality.
- Page 4-32, lines 32-34: The impact of exposure error on risk estimates is complex, with possible impacts on both the magnitude of the observed estimate but also its standard error; the discussion of this impact should reflect this complexity and include references to support its statements.
- Page 4-33, lines 23-28: Studies supporting this discussion should be referenced.
- Page 4-34, lines 6-34: This discussion pertains to temporal variability, rather than spatio-temporal variability.

Comments on Other Chapters

Chapter 8: Information from Chapter 4 should be included in Chapter 8 as well.

Dr. James Ultman

There have been numerous improvements in the organization and content of this chapter. The addition of an overall chapter introduction clearly lays out the goals of the chapter. The background information on respiratory tract anatomy included in this introduction is also a useful addition. The elimination of the sectional subdivisions between research in the previous ISA and newer research has improved the flow and readability of the text. Although a good effort has also been made to follow the technical suggestions made by CASAC during the previous ISA review, there is a need for further improvement in some of these areas. A brief summary of suggested improvements is given below, while a detailed critique is given under the individual comments appended to this document.

As its title indicates, this chapter reviews the dosimetry of ozone including its consequent reactions in epithelial lining fluid; and discusses various MOA by which ozone and its reaction products cause health effects. Some CASAC panelists felt that that MOA might be separated from this chapter, and instead be treated in conjunction with the chapters on health effects or even as a separate chapter. As currently organized, however, the final two sections of the chapter provide a useful discussion of intersubject variability and animal homology in the context of MOA along with dosimetry. The authors should strive to improve the integration between the four sections within the chapter as well as their linkages to chapters 6 and 7 on short-term and long-term health effects.

Although dosimetric principles have been better explained in this second draft of the ISA, further clarification is needed. Early in the chapter, there should be a listing and definition of the various dose metrics; these definitions should be used consistently throughout the chapter. Also, the connection between dosimetry principles, and theoretical or experimental observations of dose distribution should be discussed in more detail.

There is also the question of whether ozone alone or toxic products of its reaction with endogenous substrates is responsible for adverse responses; the chapter emphasizes the importance of reaction products far more than ozone. This orientation relies heavily on theoretical computations suggesting that ozone reaction in the epithelial lining fluid is so fast relative to its diffusion rate that unreacted ozone cannot penetrate to underlying epithelial cells. Yet, there is no description of these computations in the chapter, and no discussion of the underlying assumptions. In fact, there is literature indicating that the liquid lining layer is so thin in some parts of the respiratory tract that ozone might indeed reach underlying tissues.

Observations of O3 uptake and its distribution between regions of the respiratory tract have been made by a variety of techniques. The results of such studies on humans are summarized in table 5-1 with footnotes that attempt to capture the differences between the measurements and their interpretation. I suggest that the authors provide more detail regarding the design of these studies directly in the text. They may find one of my previous publications helpful (Handbook of Human Toxicology, edited by E. Massaro, 1997, pp 494-500). In that article, figure 1 provides a visual rendering of alternative ozone sampling strategies. Table 1A contains virtually the same O3 dose information as table 5-1 in the ISA while also presenting similar information for animals.

Detailed Comments:

Page Line

5-1 12 Change “is” to “are”

5-1 16 Change “relevant” to “related”

5-2 fig 5-1 The arrow between inhaled dose and tissue dose suggests that O3 can be absorbed without the need for transport through the ELF. Does this mean that there may be some “dry” spots on the epithelial surface? Some explanation in the figure caption would help.

5-2 fig 5-1 Change caption to read: “Schematic of the O3 exposure and response pathway. O3 transport follows a path from exposure concentration, to inhaled dose, to net dose, to the local tissue dose. Chapter 5 discusses the concepts of dose and modes of action that result in the health effects discussed in Chapters 6 and 7.”

5-2 10 Change “to the concentration of” to “to the quantity of”

5-2 1-13 This paragraph still needs some fine tuning. In particular, it is important to define the different doses that will be used in the chapter. I suggest that definitions of the following terms be incorporated in this paragraph and tied into figure 5.1. It should also be mentioned that the “net dose” represents the O3 that is available for reaction with tissue. The other definitions of dose are more-easily measurec surrogates for the net dose.
1) Exposure concentration.
2) Effective (or inhaled) Dose=concXmin.ventXtime
3) Net Dose=amount or rate of entry of O3 across the gas/ELF interface.
4) Tissue Dose=amount or rate at which O3 or its reaction products reach target tissue sites.

5-5 3 Change “its effective dose” to “its tissue dose”

5-5 7 Change “surfactant.” to “surfactant solution.”

5-5 10-12 It is premature to use the term "uptake" in this paragraph because it is not defined until the next paragraph.

5-5 10-11 Change “Ozone uptake…termed reactive absorption” to “Ozone dose is directly related to the coupled diffusion and chemical reactions occurring in ELF, a process termed reactive absorption.”

5-5 11-12 Change “Thus, the uptake...is related to both” to “Thus, O3 dose depends on both”

5-5 13-15 Delete the first sentence. Change the second sentence from “Ozone uptake is affected by complex interactions between a number of major factors including RT morphology…” to “Ozone **dose** is affected by complex interactions between a number of **other** major factors including RT morphology,”

5-5 30 Add the sentence “Measurements of O3 dose have been inferred from simultaneous measurements of airflow and O3 concentration at the airway opening of the nose or mouth (Weister,

1996; Nodelman and Ultman, 1999) as well as at internal sampling catheters (e.g., Gerrity et al., 1988,1995)" between the existing sentences "…O3 dosimetry." and "One method…"

5-5 32 Change "The O3 in the breath that is removed during the breathing period is termed" to "The difference in the amount of O3 inhaled and exhaled relative to the amount inhaled O3 is termed"

5-6 2 Change "fractional uptake of O3" to fractional absorption of O3"

5-6 3 Change "LRT(F_{LRT}) are presented.." to "LRT(F_{LRT}) relative to the amounts of O3 inhaled into the region are presented.."

5-6 5-10 The existing paragraph inadequately dispersion and the relative importance of different transport mechanisms in different airways. I suggest substituting the following paragraph:
"The three-dimensional transport of O3 in the lumen of an airway is governed by bulk flow or convection and diffusion. When modeled as a one-dimensional process in which the radial profiles of axial velocity and O3 concentration profiles are flat, O3 transport along an airway lumen occurs by convection, axial diffusion and a coupled diffusion-reaction process called dispersion. Simultaneously, O3 diffuses into the ELF where it undergoes radial diffusion and chemical reaction (Figure 5-3c) (Miller, 1995). The relative importance of these transport mechanisms varies among RT regions for a given level of ventilation in any species. In the URT and major bronchi, bulk airflow tends to be the predominant mechanism for axial transport in the airway lumen, and diffusion dominates chemical reaction in the ELF. However, in the alveolar region of the lung, diffusion is the major gas transport mechanism while reaction dominates in ELF."

5-7 7-11 Similarly, these sentences give an inadequate explanation of dispersion. I suggest changing lines 7 to 11 with the following text:
"profile and diffusion. When air flows through an airway, O3 located near the tube center moves faster than O3 near the tube wall where frictional forces retard the flow. This non-uniformity in the radial profile of velocity gives rise to an axial spreading or dispersion of the O3 that operates in parallel with bulk flow and axial diffusion (a process caused by the ever-present Brownian motion of individual O3 molecules). The shape of the velocity profile is affected by the flow direction through bifurcating airway branches (Schroter and Sudlow, 1969). The velocity profile is nearly parabolic during inhalation but quite flat during exhalation. Thus, there tends to be greater axial dispersion during inhalation than during exhalation. Dispersion also depends on the nature of the flow, that is, whether it is laminar (i.e., streamlined) or turbulent (i.e., possessing random velocity fluctuations). Because turbulent flow flattens velocity profiles, it may actually diminish dispersion. In humans, turbulent flow"
5-7 19-22 Change the last two sentences of this paragraph to
"Gas molecules close to the alveolar-capillary membrane have almost zero convective velocity with respect to the membrane, and this creates a substantial boundary layer resistance to O3 transfer across the gas-ELF interface. Thus, the transport of O3 through the ELF has a more important role in the peripheral lung than in the TB region."

5-7 6 This paragraph would be a logical place to explain how principles can be used to explain simulation results or data. In particular, how do the expanding summed airway cross-sectional area, increasing surface-to-volume ratio, and decreasing mucous thickness with increasing generation contribute to differences in axial transport and lateral absorption in different lung regions. In

combination with changes in mucous thickness, how do these effects explain the tissue dose distribution (predicted by the models and observed in the O_3-18 studies) and the net dose (predicted by the models)?

5-8 28 Change "nonlinear reaction kinetics could result" to "non-linear kinetics of O3 uptake fraction"

5-9 3 Change "and 46% between the mouth" to "and 46% during a complete breath in which an O3 bolus penetrated between the mouth"

5-9 6 Replace this line by "resulted because these investigators measurements were based on inhalation alone or was caused by O3 scrubbing by the mouthpiece."

5-9 14-15 Change "(i.e., flow rate…) was" to "(i.e., flow rate×exposure concentration×(1- nasal absorbed fraction)) was"

5-9 25 Change "removes half" to "removes about half"

5-9 32-34 In order to compare the reliability of net dose compared to tissue dose, this paragraph should be expanded. In particular, the O3-18 measurements reveal maximum damage in the CA region and less damage in the more proximal and more distal airways. This is consistent with distribution of O3 tissue dose predicted by single-path models, and suggests that O3 tissue dose is a good predictor of O3 damage. On the other hand, some of the damage might be due to toxic reaction products. The net O3 dose can be an indicator of such products, particularly when the formation of these products is rapid (e.g., in the extreme of an infinitely fast reation, all the O3 that crosses the gas-ELF interface is converted to product before reaching the ELF-tissue interface).

5-10 12 Change "uptake was" to "uptake efficiency was"

5-10 31-33 Replace these lines with
"reaction rates of O3 are proportional to the O3 concentration. As mentioned above, a weak negative relationship between O3 concentration and uptake efficiency was reported for the nasal cavities by Santiago et al., 2001. Rigas et al. (2000) also found a weak but significant negative dependence of O3 concentration on RT uptake efficiency in exercising"
5-11 4-5 Replace these lines with
"computational fluid dynamics model was created to investigate O3 transport in a single airway bifurcation (Taylor et"

5-11 13 Replace line 13 with
"child. This model predicted velocity distributions that were consistent with the earlier work of Schroter and Sudlow (1969), and also reported O3 concentration and wall uptake distributions. The model"

5-12 6-7 Not clear why this particular change was singled out to emphasize. Therefore, either delete the sentence or broaden it to other conditions.

5-13 7 Delete "URT"

5-13 31 Change "the TB" to "the URT and TB"

5-14 32 Change “the upper airways” to “these airways”

5-15 27 Sawyer studied the nasal cavities only. I expect that "1.6-fold higher delivered dose rate to the lungs" was an inference made from Sawyers results. If so, this should be stated.

5-28 31 Change “the product of airway resistance and thoracic gas volume” to “the ratio of airway resistance to thoracic gas volume”

5-14 25 The study of Hu et al.(1994) was not done under exercising conditions. Rather, the inspired and expired flow rates approaches those attained during exercise.

5-68 10 Chang “airflow patterns such that major airflow streams are created” to “airflow patterns, particularly the shape of major airflow streams.”

Dr. Sverre Vedal

Preamble

The Preamble serves its purpose. I have only minor points:

p. lvii, line 17. It's not clear from what is written how multicity studies provide insight into confounding.

p. lx, Table 1. Specificity. This "criterion" is more intended to refer to a cause having a specific effect rather than an effect having a specific cause, as written. It has become clear that this "criterion" is not very applicable to the air pollution setting where there is evidence that a single pollutant, such as ozone, causes a myriad of effects.

p. lxiv. Much of this section seems repetitious of points made earlier: dose-response, coherence across study designs and different fields of enquiry. Also, I wouldn't single out life stage as somehow distinct from subpopulations. Each life stage is simply a subpopulation that may have increased sensitivity.

Executive Summary

This executive summary is reasonably faithful to the information provided in the body of the ISA, with the rare exception. Of note, it seems that it is being claimed that UV-B radiation causes no health effects (Table 1-3), when these are clearly present (and documented on p. 2-48), and were well appreciated at the time of the previous review.

Some points need to be clarified. First, ozone exposure has only been relatively consistently associated with total and cardiopulmonary mortality in the setting of short-term exposure. This is not the case for long-term exposure. The reference to consistent associations in Section 1.6.1 therefore needs to be qualified. Second, the lack of a discernible threshold in the concentration-response relationship is an often-repeated refrain. The evidence for this is largely based on epidemiological findings. Even though the human clinical findings, specifically on level of lung function, have demonstrated effects at lower exposure concentrations, there is evidence that effects do not occur at a concentration of 40 ppb, implying a threshold.

Section 1.6.5. Ozone Concentration-Response Relationships. Here, as elsewhere in the ISA, we find the statement that there is "no indication of a threshold for O3 concentrations greater than 30 or 40 ppb." This ignores the findings from human clinical studies showing not effects at 40 ppb.

Section 1.9. Conclusion. The statement that "populations identified as being at most risk for O3-related health effects are individuals with influenza/infection, individuals with asthma, and older age groups" is too strong. Preferable wording would be something like there are some subpopulations that exhibit "potentially increased sensitivity" to ozone (eg, p. 6-139, line 25 and as used in the Integrative Summary).

Fig. 1-1 (also shown as Fig. 2-1, p. 2-7) takes some figuring out. The role of VOCs in potentiating NO2 formation is here, as is O3 quenching, but both take some searching to identify.

Ch. 2: Integrative Summary

This Summary is generally well done. I have a few issues:

1. I would have thought that one very policy-relevant question for welfare effects (p. 2-3) is that of time period of effects. This information is critical to distinguishing the averaging period and form of the secondary standard as distinct from those of the primary standard.

2. I like the attempt at including both 2006 conclusions and current conclusions in Table 2-1 (p. 2-18). However, some 2011 concluding points are uninformative, eg, "suggestive of a causal relationship" and some are not correct (see point 4 on respiratory symptoms [Where newer findings weaken earlier conclusions] below).

3. I also like Fig. 2-3 (p. 2-22) with the incorporation of evidence from studies and the types of studies (eg, tox, epi, clinical) being identified.

4. The statement on "asthma as a factor affecting risk" to ozone (p. 2-32, line 10) ignores evidence from human clinical studies that largely shows no difference in effects on asthmatics and non-asthmatics.

5. The statement on threshold is misleading (p. 2-33, line 23). The data referred to show an effect at 60 ppb, but not at 40 ppb. This is not the same as saying "Recent studies provide evidence for a smooth C-R curve without indication of a threshold in young healthy adults exposed …. to O3 concentrations between 40 and 120 ppb."

Ch. 6: Short-term exposure effects

Respiratory:

Arguably, the most important new findings relating to respiratory effects of short-term ozone exposures are from more recent human clinical studies of lung function responses showing effects at 0.60 ppm, but not at 0.40 ppm.

1. <u>Pulmonary function responses</u>.

i) It seems clear that there is likely some bronchoconstriction from ozone exposure, possibly only small airways effects, but that this must be a relatively trivial effect, and has not been demonstrated using the low concentration protocols. The reduction in FEV1 is neither prevented nor helped by inhalation of a bronchodilator or treatment with corticosteroids, suggesting that bronchoconstriction does not contribute, or is possibly just affecting small airways. My sense is that prominent reference to the contribution of bronchoconstriction to the acute lung function response (eg, in the Summary, p. 6-22, line 20; p. 6-4, line 1) reflects the difficulty the research and policy community has in accepting that this effect of ozone is entirely, or predominantly, due to triggering of airway receptors and neural responses.

ii) I somewhat reluctantly agree that one needs to use the post-filtered air exposure with exercise in assessing acute ozone effects on lung function (p. 6-4, lines 30-37). The result, however, is that the effect of ozone exposure is then essentially one of causing less improvement in FEV1 with exercise. This naturally brings up issues as to the adversity of this response.

iii) Ozone has been the "poster child" for the [concentration x time x minute volume] unifying exposure concept for a long time. It's confusing here when this point (p. 6-8, line 19) is followed closely by a discussion of the differential effects of a triangular vs. square wave exposure protocol. Both can't be completely true.

iv) I wonder whether there shouldn't be more discussion of the relevance of the acute lung function response in the chamber studies. There's a drop in level of lung function that occurs during a 6.6-hr exposure with moderate exercise when exposed to 0.60 ppm. These are conditions that are not often experienced by those for whom such a drop might be meaningful, ie, those with severe asthma or with COPD. Motivation for the relevance might be provided by the panel studies. Better linkage is perhaps warranted.

2. Sensitive (or less sensitive) subpopulations.

i) The evidence that asthmatics are particularly sensitive to the respiratory effects of ozone exposure is pretty weak. Studies that only examined subjects with asthma do not address the question of enhanced sensitivity (section "Children with asthma, p. 6-33).

ii) I think the correct characterization at this time is that there are some subpopulations that exhibit "potentially increased sensitivity" to ozone (p. 6-139, line 25). The inclusion in the list of sensitive subgroups in the Summary section (6.2.9), such as those using corticosteroids, those with current URI, older adults with bronchial hyperresponsiveness, and those with elevated BMI or certain genetic polymorphisms, largely on the basis of studies in Mexico City, is not warranted.

iii) The identification of healthy children as an at risk population is a little weird (p. 6-46, line 10).

3. Selective reporting and highlighting of positive findings and studies. While this style has been much more prominent in previous ISAs, there remain some vestiges in this latest incarnation. Examples:

i) The multi-city Canadian study by Stieb et al (p. 6-126) on COPD and asthma ED visits only highlight lag 2 findings;

ii) What is the justification for dedicating a figure to the Seattle findings on asthma ED visits (p.6-130)? This is a very selective highlighting of results.

4. Where newer findings weaken earlier conclusions.

One instance where newer study findings potentially weaken conclusions that were drawn in the 2006 ISA is, somewhat surprisingly, that relating to respiratory symptoms and medication use in asthmatic children (p. 6-86). Newer multi-city studies of symptoms in asthmatic children (Schildcrout 2006; O'Connor 2008), which should arguably carry the most weight, are not convincing or show no effects (Figure 6-11, p. 6-88 and Figure 6-11, p. 6-92). The conclusion on p. 6-100, lines 8-10, regarding respiratory symptoms and medication use in asthmatic children, and in the corresponding part of Table 2-1 (Respiratory symptoms and medication use – 2011 conclusions), can therefore be questioned. Findings from these newer studies should either be criticized and given less weight, allowing the current conclusions to stand, or else given appropriate weight and allowed to influence the conclusions.

5. Miscellaneous.

i) I'm not sure that describing a 5% within-day variability in lung function as clinically meaningful is correct (p. 6-14). Such variability may indicate some disease state, or may be outside normal variability, but the actual variability itself is unlikely to be of clinical significance.

ii) Figure 6-6 (p. 6-35) shows little support for the statement regarding decrements in FEV1 in children with asthma (p.6-33, line 18).

iii) The description of the APHENA findings (pp. 6-114 to 6-117) is complex; admittedly, the study itself and its findings are complex. Some bottom line conclusions are needed.

iv) The attempt to explain absence of associations in outpatient/doctor visit data (p. 6-131, lines 34-35 and p. 6-132, lines 24-27) is unconvincing. It is not clear whether these studies are restricted to unscheduled visits. If not, that is a more likely explanation.

Non-respiratory:

i) Highlighting a French study on ischemic stroke with positive findings with a plot demonstrating dose-response (Fig. 6-21, p. 6-153) puts more emphasis on these findings than is merited.

ii) The Gong 1998 study (p.6-143) did show controlled human exposure effects on increasing heart rate, not just on blood gases.

iii) The claim that "there is no apparent biological mechanism to explain the association observed for short-term O3 exposure with cardiovascular mortality (p. 6-183, line 21). I would argue that neural autonomic effects could be one mechanism for CV effects, as could pulmonary inflammation, just as it is in the PM setting.

Mortality:

p. 6-215, line 1. The point about the distinction between effect modification and interaction is not necessary, subtle and not widely acknowledged.

Minor:

p. 6-13, line15. Adams footnote should be 1 instead of 5?
p. 6-15, line 35. The inflammation discussion should not be in this lung function section.
p. 6-92. Table 6-120 and Figure 6-12. The Rabinovitch 2004 study should be included here.
p. 6-123. Edit title "Averting Behavior"
p. 6-14, line 2. editing needed.

Ch. 7: Long-term exposure effects

1. Introductory. There are largely two new important observational study findings that have been reported since the previous review that potentially modify the previous conclusions: 1) new-onset asthma in children and long-term ozone exposure in the CHS cohort and 2) respiratory mortality and

long-term ozone exposure in the ACS cohort. Findings from the recent toxicological study on atherosclerotic plaque size in hyperlipidemic mice are also important.

2. The CHS cohort findings. The CHS cohort still provides the most definitive data on long-term ozone exposure and longitudinal lung function growth, finding no association with ozone as opposed to the other pollutants considered. Regarding new-onset asthma, the earlier finding from this cohort was that number of outdoor sports was associated with new-onset asthma, but only in high ozone communities. This finding was only moderately compelling, being hampered by the relatively small number of cases, and by the observation that participation in tennis drove most of the association. The new findings on new-onset asthma take a gene-environment interaction approach to a larger number of cases (n=160). The emphasis is on gene main effects, somewhat unfortunately, rather than on the ozone exposure main effect, which ignores the fact that modification of ozone effects by genetic polymorphisms does not require a gene main effect. That is, genes that influence new-onset asthma may have nothing to do with how ozone might cause new-onset asthma. Having said that, the genes assessed (reported) in the CHS study (HMOX-1 and GSTP1/GSTM1) might well be of interest in influencing ozone effects. The primary finding is that the protective gene main effect is lost in the higher ozone communities (Figure 7-1, p. 7-5), a finding that was replicated in another part of the cohort. The more important finding, from the perspective of usefulness in this setting relating to policy, would have been a demonstration of an ozone main effect, with secondary modification of the ozone effect by genetic polymorphisms. Effect modification, it can be argued, should only be explored when a main effect is first observed, although in the gene-environment setting, strong modifying effects of a relatively unusual polymorphism, it could be argued, might not be reflected in an exposure main effect. Also, in the study of traffic effects on new-onset asthma, no effects of ozone were observed (p. 7-6, lines 23-29). The bottom line, however, is that I nevertheless agree with the causal assignment for respiratory effects.

3. The ACS Study. The ACS study played a central role in setting the annual standard for PM2.5, so findings on ozone effects in this cohort need to be considered seriously. Given that this is the only evidence at this point, I agree with the causal determination of "suggestive."

4. Endpoints caused by both short- and long-term exposure. Some endpoints, such as ED visits or hospitalizations, can be caused by both short-term and long-term exposure. Studies typically identify an exposure metric, and conclusions are drawn relative to that metric. When associations are observed, this results in a type of self-fulfilling prophesy regarding the temporal features of exposure, but unfortunately provides little insight into the temporal features that are most critical into producing the associations. Specifically, when it is claimed that long-term exposure to ozone is associated with increased ED visits or hospitalization, and only long-term exposure metrics are employed, it is not known whether short-term or long-term exposures are responsible. Control for short-term exposures would implicate long-term exposure.

Dr. Kathleen Weathers

Charge Question for Chapters 1 and 2

Please review and comment on the effectiveness of these revisions. Please comment on the extent to which Chapters 1 and 2 comprise a useful and effective approach for presenting this summary information and conclusions. Please recommend any revisions that may improve the scientific accuracy of these summary sections and the conclusions therein.

"Front" matter Comments:

The revisions on the first three sections are very useful. Kudos to the EPA. However, I still find the naming of the "front sections" somewhat non intuitive (e..g, Chapter 1=Executive Summary).

Preamble, lxv, line 17: "….a challenge to the quantification of exposure-response relationships for ecological effects is the great regional and local variability in ecosystems." This comment suggests that spatial heterogeneity is the major issue. Equally challenging is the temporal variability in ecological systems, which is also big. Biology, whether human or not, responds nonlinearly to its environment, and it plays out temporally and spatially.

Chapter 1:

My overarching comments have to do primarily with the integrative and/or conceptual figures. I suggest that some specific attention be paid to modifying them so that they become more useful.

The chapter could use thorough editing. I found much of the text to be rather awkwardly written (and/or punctuated) and not particularly clear.

Section 1.2 Scope: 4th line from bottom—I think that the phrase "entire body of relevant literature" should be qualified: Peer reviewed literature? Published? Agency reports? All of the above?

Section 1.3.

The readers might be reminded of the spatial extent of stratosphere and troposphere when the terms are first used, for example, troposphere (from ground level to xxkm….)

Smaller spatial scale (2nd para under Figure 1-1).

The schematic overview (Fig. 1-1-- and also again as Fig 2-1) is confusing to me. First, what's the significance of the colors (red vs blue, vs graded blue)? It's not clear. Second, similar to the comment above, some scale information would be helpful (e.g., approximate distances for troposphere and stratosphere, perhaps some information on relative speed of reactions). I'm also unclear to what "rainout deposition" refers—nitric acid? Also to what does aerosol uptake refer, and is it really gaseous uptake that is meant (but, again, of what?). Finally, the figure contains a mix of processes (e.g., reactions with UV), effects (e.g., ozone hole), and avenues of effects (aerosol uptake), which I find a little confusing.

When the figure is modified, the figure legend should also be made more specific and informative (ditto for all of the figures in this document).

Chapter 2:

This chapter misses an opportunity for true integration: across the whole of the ISA, across disciplinary lines, across various tools (modeling, scaling models up and/or down, the integration and use of models and field studies/empirical data). I think that it would be very useful to add "integrative" conceptual figures as well as an overarching section that is truly integrative.

See comments about Fig. 1.-1 (and therefore 2-1), above.

The CASTNET description should be checked for accuracy. CASTNET is a very important national network for measuring and tracking air chemistry trends and continental contrasts; it does monitor air concentrations of several pollutants of interest, and, up until recently, CASTNET modeled components of dry deposition, however it does not measure dry deposition.

2.3.4: It's unclear to me on what basis the CSAs were selected. It's also unclear to me what "closer analysis" means. The poor correlations for some regions beg the question of whether the groupings are relevant/defensible.

2.5: Upon inspiration?!

Charge Question for Chapter 9

Please comment on the reorganization and content of this chapter and the adequacy, scientific soundness, and usefulness of the material presented. Please recommend any revisions to improve the discussion of key information.

This version of Chapter 9 reads quite well. However, there are sections that could benefit from clarification.

General comments:

As is pointed out in the document, ecosystems can be (spatially) small or large, depending upon the question and the boundaries (assigned logically and defensibly, but still assigned by a person). However, throughout the text, ecosystem "scale" appears, which is confusing. I have noted a few places below where (and how) something else might be substituted in; I suggest changing it throughout the document. I also think being as explicit as possible when referring to scale, whether it is temporal or spatial, will make the text much less ambiguous.
I'm a little confused by places in the document that state "…since the 2006 Ozone AQCD, there is additional evidence" and then invoke studies from the 1990s and early 2000s.

Specific comments:

Figure 9-1: see comments below about the use of "endpoints."

9-36, Summary. I think it might be useful to put the "needs" together in this section.

9-39, lines 16+: This section could use some editing. Here are a few suggestions:"Ecosystems *can be described, in part,* by their structure, i.e., the number…", (line 26) "Plants, via such processes as photosynthesis, respiration, C allocation, nutrient uptake and evapotranspiration, affect energy flow, C and nutrient cycling, and water cycling.

9-40, lines 1-4: why isn't nutrient cycling included?

9-40, lines 9-13: delete.

Section 9.4.2: The header here seems not quite right. The section might be more appropriately titled something like: "Ozone exposure and Plants: visible foliar injury and use as biomonitors.

Hasn't ozone injury been linked to reductions in aesthetic value of landscapes? If so, it should be noted.

9.4.2.2. Summary, 9-45, line 2: but, what is new evidence of the correspondence of foliar injury and high ozone levels? I'm not convinced that the final statement is described as clearly as it might be in the section.

9.4.3., 9-45, line 19: suggest using the "stand" scale, not ecosystem scale. Further, lines 19-21: "….translate to the *stand* scale, and result in changes…

There are several places throughout the chapter where a simple phrase reminding the reader of the salient results of the previous AQCD would be a helpful addition, for example: 9-48, line 22 "…the conclusion of the previous AQCD *that…?*" and Page 9-47, line 27 "….were evaluated in previous AQCDs *demonstrating that…?"*

Page 9-47, paragraph starting on line 30: Endpoint does not seem to be the right word or concept here. Isn't it a metric? For example lines in 32-33, is the point that effects on biodiversity are as important as C fixation? Or that biodiversity can affect C fixation?

9.4.3, lines 20 and 21: I'm not sure that demonstrating the relevance of knowledge gained from trees grown in open-top chambers is an important bottom line (as part of the Summary).

9-54: Make clear the range of spatial scales that "local, regional and global scales" are referring. I also suggest adding the definitions of and relationships among GPP (and Photosynthesis if it is different from GPP in these studies), NEP, NPP R (auotrophic and heterotrophic) at the beginning of the discussion. Also, NEE, etc.. (especially since it is invoked in the Summary). I think that describing the results of the various studies could be made clearer and more comparative if you do so.

9-57: Summary, line 11: To what does "reduced ecosystem productivity" (e.g. NEP—see comments above about defining, and using consistently, terms).

9.4.4: Similar to the comment above, I suggest defining growth, yield and any related terms at the beginning of the section. The definition could go in the Figure/Table legend, in fact.

Figure 9-7: Fix legend.

9-51, line 4 "…changes in productivity at the ecosystem scale." See comments re: ecosystem scale.

Table 9-2: consider adding the spatial resolution of each model (as is done for TEM) for each of the models.

9.4.3.5. Summary: There's another reference to "ecosystem level." Also, please be specific (line 11 as well as lines 30-32)—which productivity? Whether it is GPP or NEP, for example, makes a difference.

Table 9-3: I find this a useful table. Add ecosystem type(s) to each of the studies.

9.4.6: Consumption (line 24)? Allocation seems a more appropriate word.

9-74, line 29: Ca (vs calcium ion).

9.4.6.3: An increase in root mortality and change in turnover rates would be indirect effects. This is an unclear sentence (lines 27,28).

9.4.6.4: It seems to me that pools and fluxes are not well distinguished in this section.

9.4.6.5: I found this section very confusing. If cores are brought from an anaerobic into an oxygenated environment they should/would be significantly impacted.

9.4.6.6: Summary (line 8). Below-ground processes are fueled by C, but microbes drive the processes. There's some more confusion in this section about what "ecosystem level" responses are, and are not (ecological might be a logical substitution; see comments above).

9-86, lines 28,29): The summary sentence seems a bit too broad given the caveats in the preceding section (community composition vs some qualification of which communities).

9.4.8..3: Rather than physical factors, why not simply say: temperature, light and moisture?

Table 9-8: The N additions range from reasonable to outrageous (436 kg/ha/yr), unless of course, these additions mimic commercial watermelon N applications.

The Summary (9.6.4) was very clear and will be quite useful, as was the summary table (9-17).