UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

February 10, 2006

EPA-CASAC-06-003

Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Subject: Clean Air Scientific Advisory Committee's (CASAC) Peer Review of the Agency's *Air Quality Criteria for Ozone and Related Photochemical Oxidants (Second External Review Draft), Volumes I, II, and III*, (EPA/600/R–05/004aB, bB, and cB, August 2005)

Dear Administrator Johnson:

EPA's Clean Air Scientific Advisory Committee (CASAC or Committee), supplemented by subject-matter-expert Panelists — collectively referred to as the CASAC Ozone Review Panel (Panel) — met in a public meeting held in Durham, NC, on December 6-7, 2005, to conduct a peer review of the Agency's revised *Air Quality Criteria for Ozone and Related Photochemical Oxidants (Second External Review Draft)*, *Volumes I, II, and III*, (August 2005), also known simply as the 2nd draft Ozone Air Quality Criteria Document (AQCD). The current Clean Air Scientific Advisory Committee roster is found in Appendix A of this report, and the CASAC Ozone Review Panel roster is attached as Appendix B. The charge questions provided to the Panel by EPA staff are contained in Appendix C to this report, and Panelists' individual review comments are provided in Appendix D.

The members of the CASAC Ozone Review Panel were generally pleased with the high quality of this 2nd draft Ozone AQCD and compliment the Agency staff on their efforts. The members of the CASAC Ozone Review Panel found that Agency staff had been responsive to the Panel's comments on the review of the first draft. The Panel expressed two general concerns, one related to consistency within the document, and a second concern that both positive and negative studies be given the same careful consideration. This letter provides comments and recommendations from the Committee as a whole related to each chapter in the 2nd draft Ozone AQCD, with detailed review comments from individual Panel members attached in Appendix D. Finally, as discussed below, after EPA issues the final Ozone AQCD on February 28, 2006, the CASAC will determine whether there is a need to convene a public meeting to conduct any additional review of Chapter 8, the exposure and human health effects integrative synthesis.

1. Background

The CASAC, comprising seven members appointed by the EPA Administrator, was established under section 109(d)(2) of the Clean Air Act (CAA or "Act") (42 U.S.C. § 7409) as an independent scientific advisory committee, in part to provide advice, information and recommendations on the scientific and technical aspects of issues related to air quality criteria and national ambient air quality standards (NAAQS) under sections 108 and 109 of the Act. Section 109(d)(1) of the CAA requires that EPA carry out a periodic review and revision, where appropriate, of the air quality criteria and the NAAQS for "criteria" air pollutants such as ozone. The CASAC, which is administratively located under EPA's Science Advisory Board (SAB) Staff Office, is a Federal advisory committee chartered under the Federal Advisory Committee Act (FACA), as amended, 5 U.S.C., App. The CASAC Ozone Review Panel consists of the seven members of the chartered (statutory) Clean Air Scientific Advisory Committee, supplemented by sixteen technical experts.

EPA is in the process of updating, and revising where appropriate, the AQCD for ozone and related photochemical oxidants published in 1996. Under CAA sections 108 and 109, the purpose of the revised Ozone AQCD is to provide an assessment of the latest scientific information on the effects of ambient ozone on the public health and welfare, for use in EPA's current review of the NAAQS for ozone. This meeting was a continuation of the CASAC Ozone Review Panel's peer review of the revised Ozone AQCD in this present NAAQS review cycle for ozone. On January 31, 2005, EPA's National Center for Environmental Assessment, Research Triangle Park, NC (NCEA-RTP), within the Agency's Office of Research and Development (ORD), made available for public review and comment a First External Review Draft of a revised document, *Air Quality Criteria for Ozone and Related Photochemical Oxidants (First External Review Draft), Volumes I, II, and III*, (EPA/600/R–05/004aA, bA, and cA, January 2005). The CASAC Ozone Review Panel met in a public meeting held in RTP, NC, on May 4-5, 2005 to conduct its initial peer review of the 1st draft Ozone AQCD. The Panel's letter/report to you from this May 2005 meeting, dated June 22, 2005, is found at the following URL: http://www.epa.gov/sab/pdf/casac_ozone_casac-05-010.pdf.

2. CASAC Ozone Review Panel's Peer Review of the 2nd Draft Ozone AQCD

The peer review of the EPA's second external review draft AQCD for ozone and related photochemical oxidants took place in a public meeting held in Durham, NC, on December 6-7, 2005. The members of the CASAC Ozone Review Panel were generally pleased with the improvement in the 2nd draft Ozone AQCD and found that Agency staff had been responsive to the Panel's comments on the review of the first draft. The Panel was supportive of the new format in which all of the main chapters were included in Volume I and the annexes were contained in Volumes II and III. The Panel suggested that in the future, electronic links to the appropriate material in the annexes be included in Volume I, so that a reviewer looking at the electronic version of the document (*i.e.*, on CD-ROM or through EPA's web site) could quickly access the annex material. The Ozone Review Panel also supported the addition of an Executive Summary at the beginning of Volume I.

The Panel expressed two general concerns. One concern was related to consistency within the document. Some of the same information is now given in three places: the Executive

Summary, the main text, and the annexes. EPA staff needs to check carefully to be sure there is consistency across all three parts of the documents. Individual review comments prepared by Panelists indicate some of the inconsistencies caught by the Panel, but there was a concern that a careful overall review by the authors was required.

A second concern was that both positive and negative studies of associations between ozone concentrations and health outcomes be given the same careful consideration. It is important that the Ozone AQCD does not contain an inappropriate bias emphasizing positive studies over equally well-designed studies that report a negative result in terms of adverse health effects. Avoiding this kind of selective "publication bias" becomes increasingly important as the gap between ozone ambient air quality standards and policy-relevant background (PRB) concentrations decreases.

The following paragraphs provide comments and recommendations from the Committee as a whole related to each chapter in the 2nd draft Ozone AQCD. In addition, detailed review comments from individual Panel members are attached in Appendix D.

The revised version of Chapter 2 (Physics and Chemistry of Ozone in the Atmosphere) of the Ozone AQCD is a substantial improvement on what was a good first draft. There are no major issues with this chapter although there are some minor issues that, if adequately addressed, will strengthen the chapter. As indicated by its title, this document should focus on ozone and related photochemical oxidants. Ozone is one of many photochemical oxidants that collectively dominate tropospheric chemistry. Changes in ozone precursor emissions result in: changes to ozone, other oxidants and their many various reaction products — including organic and inorganic acids and the consequent on acidification of precipitation by these acids — and formation of secondary organic and inorganic aerosols. Several Panel members also emphasized the importance of discussing oxidants in both gaseous and particle-bound phases (see detailed suggestions in Panelists' individual review comments found in Appendix D).

A recent publication that would be useful to add to the Ozone AQCD is: Docherty *et al.* (2005), Contributions of Organic Peroxides to Secondary Aerosol Formed from Reactions of Monoterpenes with O_3, *Environ. Sci.. Technol.* 39: 4049-4059. This is an important study for showing the relationship between new particle formation and the incorporation of particle-bound reactive oxygen species. Additional introductory discussion of relationships among oxidants, acidity and aerosols will help emphasize that the control of ozone precursors can lead to improvements of air quality in a variety of other areas.

With respect to ozone monitoring, there needs to be better discussion of the precision and accuracy of current generation monitors, and how the averaging process should be reflected in the setting of how attainment is determined. Rounding to the nearest 10 ppb needs to be reviewed, with a decision as to whether a tighter range (say, the nearest 2 ppb) should be used to demonstrate attainment, reflecting the improvements in instrumentation, a longer averaging period, and the need to protect human health. In particular, the shift to an 8-hour average standard reduces uncertainty as compared to a one-hour average measurement for which the original rounding to the nearest 10 ppb was determined. Thus, there needs to be a better analysis

and presentation of the ability of ozone monitors to provide accurate and precise 8-hour average values so that this information can inform policy on rounding values.

In general, Chapter 3 (Environmental Concentrations, Patterns, and Exposure Estimates) and the associated Annex have been greatly improved in the 2nd draft Ozone AQCD as compared to the first draft. Nevertheless, the Panel identified some areas that would benefit from further improvements. One of the most important is better integration between the main Chapter 3, its Annex, and the Executive Summary. The Panel also expressed some concerns regarding the use of the single global model (GEOS-CHEM) for the PRB estimation. The comparison of model outputs with actual measurements should be included in the main chapter, providing convincing evidence that this global model is suitable for the PRB estimation, especially on the regional and local scale. To the extent possible, the bias and prediction error of the models should be quantified. Also, the section regarding trends in emissions and concentrations of ozone precursors, mainly VOC and NO_x (Section 3.5), needs additional work. It might also be useful to include some illustrations of trends in different percentiles of the ozone distribution over the past 15 years. For example, have reductions in peak hourly or 8-hour concentrations been proportionately greater than changes in average, median or 10^{th}-percentile ozone concentrations? Furthermore, in the section on human exposures to ozone, information should be provided about how the Air Pollutants Exposure (APEX) model outputs compare with personal exposures and its role in health risk assessment. Some panel members expressed concerns with uncertainties introduced by the kriging procedures used for mapping ozone fields. Others noted that the traditional shaded "county plots" are not well-suited for conveying useful spatial information.

Chapter 4 (Dosimetry, Species Homology, Sensitivity, and Animal-to-Human Extrapolation) is greatly improved from the 1^{st} draft Ozone AQCD. Information on ozone dosimetry, species homology, sensitivity and animal-to-human extrapolation provides a basis for the integration of animal toxicological, human clinical and epidemiological studies to assess the potential for adverse effects in humans exposed to ozone. Several topics identified by the Panel as needing to still be addressed include: (1) providing an understanding of the temporality of ozone exposures (*i.e.*, single, repeated, acute, chronic), and how such exposures can lead to alterations in the resultant biological effects; (2) discussing where the primary sites of tissue damage by ozone are located; and (3) examining chemical reaction kinetics and rate constants appropriate for predicting sites of epithelial injury when modeling the dosimetry of ozone. Panel members provided a number of individual comments on various other issues that should be easily addressed by EPA staff.

In Chapter 5 (Toxicological Effects of Ozone and Related Photochemical Oxidants in Laboratory Animals and *In Vitro* Test Systems), EPA staff have done an excellent job of incorporating into the second draft the comments and suggestions made by the CASAC Ozone Review Panel in May 2005. The Panel found this chapter well-written, well-organized, and adequately reflective of the published literature since the last version of the Ozone AQCD. The Panel suggested that a short summary of what is known from earlier studies would strengthen the chapter. The added figures clearly enhance the written text, but more descriptive figure legends are needed. The summaries and interpretations provided at the end of each subsection are also well done and informative. The revised version presents a more integrated assessment of the *in*

vivo animal data and the *in vitro* studies. The enhanced cross-referencing between findings in these studies with those presented in Chapter 6 is particularly useful.

Overall, the Panel found that Chapter 6 (Controlled Human Exposure Studies of Ozone and Related Photochemical Oxidants) represents a comprehensive scientific update and summary. The format of the chapter helps the reader understand the various types of effects seen in humans following exposure to ozone. The majority of previous comments from Ozone Review Panel members have been satisfactorily incorporated into this draft and the Panel was pleased with the progress and improvement of the draft. Some improvements suggested for Chapter 6 are as follows:

- The genetic modulation of ozone responses and the cardiovascular effects of ozone exposure in humans have been more fully-addressed in this draft but the discussants on the Panel recommended several wording changes and points of emphasis (see Panelists' individual review comments).

- Salient human data from the 1996 Ozone AQCD remain key to this version of the draft Ozone AQCD and should be succinctly restated for foundation and perspective (again, see individual Panel member comments for specific examples).

- Panelists considered the need for new study data reflecting controlled human exposures to low ozone concentrations, *e.g.*, less than 0.08 ppm. A paper on this subject entitled, "Comparison of Chamber 6.6-h Exposures to 0.04-0.08 PPM Ozone via Square-wave and Triangular Profiles on Pulmonary Responses," by W.C. Adams, has recently been accepted for publication in *Inhalation Toxicology* (18:1-10, 2006). The Panel was given a preprint of that paper and considered it of sufficient importance that the Panel recommended that the Agency include this information in the Ozone AQCD and in their consideration of standards in their Ozone Staff Paper.

- It was suggested that Section 6.12.1 on "Aircraft Cabin Studies" can be deleted from Chapter 6 and inserted into ANNEXAX6.

Chapter 7 (Epidemiologic Studies of Human Health Effects Associated with Ambient Ozone Exposure) is significantly improved from the previous draft and has incorporated most of the Panel's previous constructive comments. In general, the Ozone AQCD is now a relatively balanced review of the specific topics and presents a well-formulated and logical progression of summarizing the available data. The format of moving through a summary of the 1996 data followed by the update of new studies and the breakdown of morbidity and mortality by total, disease, and specific risk categories works effectively, and represents a much-improved summary of current knowledge that is relevant to the setting of an ozone NAAQS. There are several specific suggestions in the individual review comments of Panel members attached in Appendix D.

One arena that the Committee believes should be more fully explored is the risk to outdoor workers. Very little of the literature available on outdoor workers has been included in spite of definite evidence of health impacts on this group. Another is the evidence from earlier studies of children at recreational summer programs and of young adults engaged in recreational outdoor exercise that their ozone-related decrements in lung function were greater, per unit of

ozone concentration, than those seen in controlled exposures to ozone alone in chamber studies, suggesting that other components in the ambient air pollution mixture were potentiating the effects of ozone. This additional discussion can help to explain the relatively large responses in the outdoor workers, who are also exposed to ozone as part of a complex mixture, and this whole discussion can be tied to the revisions that we called for in Chapter 2 concerning ozone as a surrogate measure for all of the photochemical oxidants.

In addition, at least one Panelist suggested that the discussion of further exploration of the birth defects data was not warranted. A number of Panel members expressed some concern that the chronic effects section could be explored more fully, although in general there was agreement that the emphasis on the uncertainty was well placed. This chapter, as well as several others, would also be improved by better linkage between the figures presented and the actual annex tables from which the figures are taken.

The Panel was concerned that EPA staff had made judgment decisions as to which papers published after the closing date of December 2005 were to be included without clearly specifying criteria that had been vetted by a wide enough group. Previous CASAC NAAQS review panels have endorsed selective inclusions of recently-published papers that add significantly to the body of data on critically-important issues. In the case of this draft Ozone AQCD, the three meta-analysis papers on daily mortality seem to warrant inclusion. The Committee, therefore, recommends inclusion of the appropriate criteria in the text of the Ozone ACQD for decisions on inclusion.

Panel members judged that Chapter 8 (Integrative Synthesis: Exposure and Health Effects) needs to be shortened and more focused on the application of data and conclusions to health effects relevant to ozone exposure levels near or below the current ozone air quality standard. A table should be added that lists all studies that demonstrate possible adverse health effects occurring at or below the current air quality standard. Following this table there should be a discussion of the strengths, weaknesses and overall value of each of the studies. A second table that lists studies showing no adverse health effects at exposure levels at or below the current ozone air quality standard should also be included. Again, the strengths and weaknesses of these studies should be clearly identified. It is important that this chapter not contain an inappropriate bias emphasizing positive studies over equally well designed studies that show no adverse health effects in response to low level ozone exposure. The summary and conclusions section of Chapter 8 needs to identify the relevance of the reported studies or conclusions to ozone exposure levels at or below the current air quality standard. For each point made, Staff should provide information regarding the relevance of their conclusion to ozone levels at or below the current air quality standard. Conclusions regarding data that address the form of the standard should be included in Chapter 8.

The Panel also commented that this integrative chapter needs to better address the plausibility of the more recent observational findings on mortality, especially cardiovascular mortality associated with low level ozone exposure. Use of toxicological findings and the Hill criteria, as was done, are important in attempting to support plausibility, but exposure issues are equally important. Specifically, this will require addressing the adequacy of ozone concentrations at central urban monitors as a measure of exposure in a population (*e.g.*, the

inactive, debilitated, or elderly) that is at the low end of the distribution of population ozone exposure concentrations. Further, since levels of ozone are more exquisitely sensitive to meteorology than those of other criteria pollutants, a more rigorous discussion of the adequacy of control for effects of meteorology in the epidemiological studies is needed. More generally, a better motivation for the utility of time series studies in providing information relevant to setting standards for individual criteria pollutants such as ozone is needed.

The discussions of cardiovascular effects and chronic effects of ozone also need to be improved in Chapter 8. Specifically, more relevant experimental findings need to be presented to support the cardiovascular effects observed in the epidemiological studies; findings on widening of the alveolar-arterial oxygen gradient or V/Q mismatch are only peripherally relevant. Also, Staff need to clarify that the evidence for ozone effects on cardiovascular hospitalizations, at this time, is inconclusive, at best. The current discussion of chronic effects does not reflect the weight of evidence on chronic effects in that inadequate weight is given to major studies in which no effects of long-term ozone exposure, either on level of lung function or on mortality, are observed.

Furthermore, the issue of the shape of the concentration-response function and of thresholds will be critical to the deliberations presented in the Ozone Staff Paper. More attention therefore needs to be paid to this issue in Chapter 8. For example, there is no attempt to bring into this discussion the implication of differences in seasonal ozone effects, which would appear to be relevant. Also, the apparent differences between the experimental and epidemiological findings pertaining to the issue of thresholds need to be addressed. Finally, given the critical importance of the exposure and human health effects integrative synthesis chapter in the development of the 2nd draft Ozone Staff Paper, after EPA issues the final Ozone AQCD on February 28, 2006, the CASAC will determine whether there is a need to convene a public meeting to conduct any additional review of Chapter 8.

The Panel commended the authors for their revision of Chapter 9 (Environmental Effects: Ozone Effects on Vegetation and Ecosystems). A significant improvement was achieved by presenting the major conclusions and scientific findings in three different formats: (1) a very brief (4-page) Executive Summary; (2) a relatively short (21-page) main chapter; and (3) a very thorough and detailed (410-page) Annex A9X. The Annex is a comprehensive compilation of scientific information published both before and after the 1996 Ozone AQCD. The main chapter provides a balanced and thoughtful summary with emphasis on current scientific knowledge about ozone effects on vegetation and ecosystems. That being said, more effort is required by the authors to ensure that the most important aspects of current knowledge are dealt with in both the main chapter and the Executive Summary, and that the scientific content and tone of all three sections are consistent with each other.

Chapter 10 (Tropospheric Ozone Effects on UV-B Flux and Climate Change Processes) provides an informative, qualitative discussion of the potential interactions between ozone, UV-B radiation and global climate change. The Panel was pleased to see EPA staff consider these complex indirect effects in the 2nd draft Ozone AQCD, notes substantial improvement from the first draft, and generally agrees with Agency Staff's conclusions that quantitative effects assessments are not currently feasible on a national basis. Since ozone efficiently absorbs both

UV and IR radiation, reductions in tropospheric ozone have a theoretical potential to lead to local or regional increases in surface UV-B flux as well as reductions in greenhouse gas climate forcing effects. Increasing UV exposures could lead to increases in the incidence of cataracts, skin cancers, and other adverse effects from suppression of immune system responses, but may also provide beneficial protective effects, including reductions in the incidence of several other forms of cancer, through increased production of vitamin D. Given the disproportionate influences from stratospheric ozone, tropospheric aerosols, clouds and human activity factors, it is not currently clear if relatively small local or regional changes in tropospheric ozone that might result from efforts to attain U.S. NAAQS would have any perceptible influence on human exposures to or effects from UV-B radiation. Complex and poorly-understood climate feedback interactions also preclude our current ability to make reliable quantitative estimates of climate change effects that might result from small local or regional reductions in tropospheric ozone. New research efforts by EPA and others will be needed to allow the Agency to provide better, more quantitative estimates of effects of tropospheric ozone on (and from) UV-B radiation and climate change in the next cycle of ozone criteria review.

The panel had no concerns relative to Chapter 11 (Effect of Ozone on Man-Made Materials).

In conclusion, the Clean Air Scientific Advisory Committee and the CASAC Ozone Review Panel encourage EPA in its continued efforts to protect the public health and our environment from adverse effects of ambient ozone and photochemical oxidants. The Committee will continue to offer its advice and recommendations to assist the Agency in meeting the mandates of the Clean Air Act. The Committee looks forward to seeing the final version of the Ozone AQCD and to its review of the 2nd draft Ozone Staff Paper. As always, we wish the Agency staff well in this important endeavor.

Sincerely,

/Signed/

Dr. Rogene Henderson, Chair
Clean Air Scientific Advisory Committee

Appendix A – Roster of the Clean Air Scientific Advisory Committee

Appendix B – Roster of the CASAC Ozone Review Panel

Appendix C – Charge to the CASAC Ozone Review Panel

Appendix D – Review Comments from Individual CASAC Ozone Review Panel Members

Appendix A – Roster of the Clean Air Scientific Advisory Committee

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)

CHAIR

Dr. Rogene Henderson, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

MEMBERS

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Mr. Richard L. Poirot, Environmental Analyst, Air Pollution Control Division, Department of Environmental Conservation, Vermont Agency of Natural Resources, Waterbury, VT

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Appendix B – Roster of the CASAC Ozone Review Panel

U.S. Environmental Protection Agency
Science Advisory Board (SAB) Staff Office
Clean Air Scientific Advisory Committee (CASAC)
CASAC Ozone Review Panel

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Dr. Rogene Henderson*, Scientist Emeritus, Lovelace Respiratory Research Institute, Albuquerque, NM

MEMBERS

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Dr. Allan Legge, President, Biosphere Solutions, Calgary, Alberta, Canada

Dr. Morton Lippmann, Professor, Nelson Institute of Environmental Medicine, New York University School of Medicine, Tuxedo, NY

Dr. Frederick J. Miller*, Consultant, Cary, NC

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* Members of the statutory Clean Air Scientific Advisory Committee (CASAC) appointed by the EPA Administrator

Appendix C – Charge to the CASAC Ozone Review Panel

SUMMARY OF SALIENT REVISIONS INCORPORATED INTO AUGUST 2005 SECOND EXTERNAL REVIEW DRAFT OF OZONE AQCD AND ASSOCIATED CHARGE QUESTIONS FOR DECEMBER 2005 CASAC PUBLIC MEETING

A. GENERAL REVISIONS

Re-sequencing of Main Chapters and Annexes. One overarching modification seen in the 2nd Draft Ozone AQCD is a restructuring of the three volumes which comprise it. Specifically, in contrast to the placing of annex materials immediately after the particular chapter to which they are related as was done in the 1st Draft (and, therefore, their being interspersed across each of three volumes), all of the main chapters of the revised Ozone AQCD (including the Executive Summary and Chapters 1 through 11) now all appear in Volume I, whereas Volumes II and III of the 2nd Draft AQCD include the annexes to the main chapters. In keeping with CASAC's advice, this emphasizes EPA's shift toward a new approach (as embodied in the newly developed Ozone AQCD) of focusing the main criteria document chapters on shorter, interpretive evaluations of literature and the inclusion of more-detailed descriptive information in annexes to the main criteria document.

> **Charge Questions – Overall.** Does this new format meet Panel members' expectations in terms of facilitating reading and comprehension of the evaluations and conclusions that are communicated in the overall criteria document materials, *i.e.*, in the AQCD's main chapters and accompanying annexes? Or, would alternative sequencing of materials to have a given annex immediately follow its relevant main chapter be more "reader friendly" and effective?

Addition of an Executive Summary. A newly-developed Executive Summary has been added to the 2nd Draft Ozone AQCD; specifically, at the beginning of Volume I. That summary is provided mainly in terms of concise bullets characterizing key findings and conclusions drawn from various main chapters of the document.

> **Charge Question – Executive Summary.** What are the Panel's views with regard to the format of the newly-provided Executive Summary and the soundness of its scientific content, including consistency of the restatement of key findings and conclusions stated in the main chapters of the document?

B. REVISIONS TO SPECIFIC CHAPTERS

Chapter 2. In addition to responding to comments on specific technical or grammatical points, a sub-section on possible mechanisms of formation of reactive oxygen species (ROS) in particulate matter (PM) was added. Studies of the formation of ROS in PM are sparse. Material from new studies of the effects of interference on ozone measurements was also added. The results of these studies indicate that effects of interfering substances can be substantial in highly-localized environments, but are not likely to be a cause for concern in typical ambient environments.

Chapter 3. Sections of Chapter 3 characterizing ozone air quality across the United States were almost entirely rewritten. Discussion of ambient air quality analyses focused on ozone in the twelve urban areas to be considered in risk assessments in the Ozone Staff Paper. Information for ozone across the range of concentrations found in ambient air was included. Additional material on observations for oxidants other than ozone, present in both gas and particulate phases, was added, based mainly on results of limited field studies for those "other" oxidants.

> **Charge Questions – Chapters 2 & 3.** Given the expanded information related to "other photochemical oxidants" in response to earlier CASAC advice, what are the Panel members' views with regard to the scope and scientific adequacy of Chapters 2 & 3? Are there any other important topics that should be addressed?

Chapter 4. Based on earlier review of this chapter on dosimetry of ozone in the respiratory tract in the 1st Draft Ozone AQCD, the CASAC recommended increased discussion about (and inclusion of more figures illustrating) basic dosimetric principles related to ozone uptake and effects. The organization of the chapter also caused some confusion as to summarization of the state of knowledge at the time of the 1996 Ozone AQCD and the evaluation of new dosimetry-related advances since then. In response to CASAC Ozone Review Panel comments, extensive revisions were made to Section 4.2 to better clarify information related to these areas.

> **Charge Question – Chapter 4.** Are there any further revisions that should be made beyond the new figures, associated discussions, and reorganization of Section 4.2 and its constituent discussions in order to adequately address the Panel's earlier concerns?

Chapter 5. In response to CASAC comments, three figures were added to Chapter 5 to better illustrate mechanisms of ozone toxicity and genetic susceptibility. NCEA staff also removed discussions of studies using high, non-ambient levels of O_3 and added caveats informing readers that events and mechanisms observed at higher concentrations may differ from those observed at near-ambient levels. Better descriptions were added of research covered in the previous O_3 AQCD. Redundancy was eliminated by placing only tables in the annex and discussions and interpretations of the research in the main chapter.

> **Charge Question - Chapter 5.** Do these added figures, additional discussions, and general reorganization of the material adequately address the concerns expressed regarding the first draft? Does the Panel have any further recommendations to improve the chapter?

Chapter 6. Numerous minor corrections and coverage of some more references were added throughout Chapter 6 (on Controlled Human Exposures to Ozone) and its associated annex in response to the first CASAC review. However, more notable revisions were made to a few sections. First, in response to concerns that genetic factors were not adequately discussed, Section 6.5.7 and its annex on genetic factors were completely revised and expanded to include a number of newer studies. Second, Section 6.9.3 on inflammatory responses in the lower respiratory tract was considered by the CASAC Ozone Review Panel to be too lengthy relative to other inflammatory response sections; in response, that section (6.9.3) has been substantially rewritten and shortened, despite inclusion of a new figure illustrating temporal patterns for various responses and coverage of several new references. Third, given the CASAC's review comments noting that Section 6.10 did not adequately address cardiovascular effects of ozone

exposure, Section 6.10 and its annex on extrapulmonary effects were revamped to include more discussion of relevant studies of ozone cardiovascular effects.

> **Charge Questions – Chapter 6.** Although there is a paucity of clinical studies concerning human genetic factors in relation to ozone effects, do revised Sections 6.5.7 and AX 6.5.7 adequately discuss the current state of knowledge and uncertainty related to the existing pertinent studies? Also, does the Panel find that Section 6.9.3 on inflammatory responses to more succinctly, yet adequately, summarize pertinent information than the previous draft? Moreover, do revisions to Section AX6.10 adequately characterize the intimate relationship between the pulmonary and cardiovascular systems, and do materials in Sections 6.10 and AX6.10 provide sufficient background information to adequately address potential cardiovascular effects of ozone as evidenced by clinical studies?

Chapter 7. The acute ozone mortality discussion has been updated and enhanced in response to comments from CASAC and the public. In addition, new literature, including three published meta analyses, has been incorporated. The examination of CVD mortality and associated morbidity studies have been updated and expanded with published literature. Efforts were also made to incorporate limitations of assessing the presence of thresholds of ozone effects.

> **Charge Questions – Chapter 7.** Do the current discussions adequately present the relationship between ozone exposure and acute mortality, and the strength and robustness of the evidence base? Are the discussions on the concentration-response relationships and the potential existence of thresholds of ozone effects improved? Are the summary statements regarding the concentration-response relationship and threshold of effects substantiated?
>
> Are acute and chronic pulmonary function outcomes clearly presented? For individual studies, are % changes in FEV_1 or PEF more uniformly presented to enhance comparison of effects among the various studies? Are presentations of the chronic studies informative and summary statements on the chronic effects appropriate?
>
> Are the revisions of Chapter 7 responsive to comments made by CASAC and the public with regard to the 1st ERD? Specifically, has the prior focus on statistical significance been redirected to effect estimates with confidence intervals or SD and include pertinent data such as sample size when necessary? Have repetitive, overly fundamental background information and cross-references to the previous PM AQCD been revised appropriately in the introduction and the interpretive sections? Are the summary of key findings and the conclusions derived from the ozone epidemiology studies focused and substantiated? In addition, have the Annex Tables been improved in regard to presentation of ozone levels and ranges, study design and limitations?

Chapter 8. This critical Integrative Synthesis chapter of the Ozone AQCD has been extensively revised in the 2nd Draft Ozone AQCD so as to present a more coherent discussion on the overall health effects associated with ambient ozone exposures. Extensive efforts have been made to characterize important pertinent information for assessing the consistency between experimental findings in human and animal toxicology studies with observational findings reported in the epidemiologic studies for both acute and chronic exposures. The discussions in section 8.2 have also been revised to present current ambient ozone air quality trends, including new information on factors affecting human exposures (section 8.3).

This information has been utilized to integrate exposure issues in the synthesis of health effects discussed in section 8.4 based on experimental toxicology studies in humans and laboratory animals (biochemical, physiological inputs) together with the epidemiologic observations. The scientific information synthesized here was utilized to evaluate and highlight biological plausibility associations presented in section 8.5 for the important epidemiological observations: respiratory morbidity; mortality (particularly with additional new discussions on cardiovascular effects); and potential susceptibility factors including potential ozone-allergen interactions associated with these observations (Section 8.6). The last section presents an overall summary and conclusions for ozone health effects.

Charge Questions – Chapter 8. How well does the revised Integrative Synthesis chapter in the 2nd Draft Ozone AQCD accomplish the desired integration of key findings and conclusions from Chapters 2 through 7, and in what ways might that chapter be further improved? In particular, are the discussions on ozone-allergen interactions sufficiently clear with regard to potential susceptibility issues? Also, how well does the revised draft of Chapter 8 provide an integrated health effects assessment for chronic effects of O_3? Do the discussions in the biological plausibility section adequately capture and synthesize pertinent key scientific information from Chapters 5 and 6 (as also summarized in Table 8-1 and Figures 8-9 and 8-10) to characterize the extent to which various O_3-induced pulmonary function/respiratory symptom effects may be considered adverse for various types of exposed human population groups (*i.e.*, as a function of age and respiratory disease status)? Lastly, are there any other important topics or issues that need to be addressed in the Chapter 8 Integrative Synthesis?

Chapter 9. An overarching recommendation from the CASAC's earlier review of this chapter on ozone vegetation/ecosystem effects pertinent to scientific bases for secondary ozone NAAQS was that it be revamped to encompass a structure analogous to that used for other chapters, *i.e.*, the focusing of the main AQCD chapter on short, interpretive evaluation of information of most relevance for derivation of criteria supporting NAAQS decision-making and allocation of more extensive, detailed descriptive materials to accompanying annexes. Appropriate revisions were done to accomplish this, with the discussions in the body of Chapter 9 in the 2nd Draft Ozone AQCD being restricted to a much shorter interpretive summary of key information and more detailed descriptive information being placed in accompanying annex materials.

A key issue addressed in the revised chapter deals with derivation of several different metrics or indices reflective of exposure-response relationships for ozone-induced vegetation damage. In its earlier review, the CASAC also recommended that EPA undertake a re-analysis of NCLAN data to determine whether 8-hour moving average ozone metrics exhibit similar vegetation exposure- response surfaces as the SUM06 ozone metric presented in the 1st Draft Ozone AQCD. In response to the CASAC's advice, statistical analyses of NCLAN data have been undertaken as a complement to the current draft of section 9.5 entitled "Ozone Exposure – Plant Response Relationships." Also of note is the addition of discussion in Chapter 9 and/or accompanying annex materials of a number of so-called Free Air Control Exposure (FACE) studies published since those covered in the 1st Draft Ozone AQCD. Besides the first charge question listed below focusing on evaluation of the adequacy of such just-noted revisions, many of the original charge questions posed for the earlier CASAC review of the 1st Draft AQCD still apply.

Charge Questions – Chapter 9. What are the CASAC Ozone Panel's views on the adequacy of the much shorter evaluative discussion now comprising Chapter 9 of the 2nd Draft Ozone AQCD? Have any crucially important new FACE studies or other crucially important types of ecological effects studies been missed? Are there any additional modifications to the main body of Chapter 9 or accompanying annex materials that would further strengthen the overall coverage and interpretation of findings related to ozone vegetation/ecosystem effects?

Chapter 10. Chapter 10, on UV-B flux and climate change, has undergone further revision to provide a concise but clear overview of key information regarding tropospheric O_3 effects on UV-B flux at the earth's surface, factors governing human exposure to UV-B and its potential human health effects. In particular, the CASAC called for — and changes were made in the chapter — to provide:

(a) tighter links between the detailed information provided on human factors governing UV-B exposure and the summary and conclusions concerning scientific basis for evaluating the role of pollutant O_3 and UV-B health effects;

(b) tighter links between Chapter 3 discussions on policy-relevant background (PRB) concentrations and patterns of elevated O_3 levels and Chapter 10 discussion of role of ozone in climate change (with text reviewing this being introduced where appropriate in Chapter 10 discussion of regional and local O_3 concentrations and trends in the context of climate forcing); and

(c) stronger statements on the evidence for and impacts of climate change (with discussion of studies concerning the evidence of GHG-linked sea surface warming published in *Science* being added, and the reader being referred to several detailed studies on the potential climate change impacts — given that a greatly-expanded discussion of this subject is seen as beyond the scope of this Ozone AQCD).

Overall, the Chapter continues to find that available evidence is insufficient to allow trustworthy quantification of the direct role of surface- level O_3 on UV-B flux and that no reasonable estimates of risks of UV-B-related human health effects due to the reduction of surface-level O_3 can be made at this time. Chapter 10 also concludes that, while it is well known that O_3 is a very effective greenhouse gas, quantification of its role as a climate forcing agent is uncertain due to its relatively short atmospheric lifetime and incomplete information on its global sources. Evidence indicates that the global atmospheric background levels of O_3 are increasing, leading to its increasing role in global-scale climate change. It seems likely, however, that due to its tendency to exist at high concentrations adjacent to the sources of its precursors, the climate impacts due to anthropogenic O_3 may be most important at regional scales.

Charge Questions – Chapter 10. Does Chapter 10 effectively discuss issues associated with quantifying: (a) the role of surface-level O_3 in determining the UV-B to which humans may be exposed; and (b) the available information on factors governing human exposure to UV-B and specific health consequences associated with UV-B exposure? Also, does Chapter 10 adequately describe the role of tropospheric O_3 in the climate system and summarize the available evidence concerning ozone's role in changing climate? Are there any additional modifications that would strengthen Chapter10?

Appendix D – Review Comments from Individual CASAC Ozone Review Panel Members

This appendix contains the preliminary and/or final written review comments of the individual members of the Clean Air Scientific Advisory Committee (CASAC) Ozone Review Panel who submitted such comments electronically. The comments are included here to provide both a full perspective and a range of individual views expressed by Panel members during the review process. These comments do not represent the views of the CASAC Ozone Review Panel, the CASAC, the EPA Science Advisory Board, or the EPA itself. The views of the CASAC Ozone Review Panel and the CASAC as a whole are contained in the text of the report to which this appendix is attached. Panelists providing review comments are listed on the next page, and their individual comments follow.

Panelist **Page #**

Dr. John Balmes

John Balmes: Review of Ozone AQCD Chapter 6

p. 6-1, lines 27-30 through p. 6-2, lines 1-7 Salient features of the 1996 Ozone AQCD re: controlled human exposure studies should include airway inflammation. The first paragraph of section 6.9.3 makes the case for why airway inflammation in ozone-exposed humans is a salient feature of the 1996 AQCD.

p. 6-4, lines 11-17 No summary of the McDonnell et al. results re: magnitude of the average effect is given to assist the reader (i.e., what is the predicted effect on FEV1 for a given C, T, and minute ventilation?).

p. 6-4, lines 22-27 The description of the Ultman et al. study should follow the remainder of the discussion of McDonnell et al. (p. 6-4, lines 28-30 through p. 6-5, lines 1-2.

p. 6-8, line 29 No subjects ever complain of "tracheobronchial airway irritation." I suggest substituting "cough and pain on deep inspiration."

p. 6-12, line 20 I would not use "bronchial hyperresponsiveness (BHR)" here or anywhere else in the chapter. First, the term, airway hyperresponsiveness (AHR), was already introduced on p. 6-8. line 31 and is used later in this chapter (6-29 and 6-30) as well as in Chapter 8. Second, small airways are involved in the lung function response to methacholine or histamine so BHR is a somewhat physiologically incorrect term.

p. 6-12, line 25 I would revise this sentence as follows: "…baseline airway responsiveness." There is no need to potentially confuse readers by substituting "reactivity" for responsiveness.

p. 6-12, line 30 I would revise this sentence as follows: "An in vitro study of isolated human bronchi has shown that…."

p. 6-13, line 11 I suggest "multiple" rather than "many" mechanisms.

p. 6-16, line 4 I would revise this sentence as follows: "Similar ozone-induced spirometric responses of asthmatic and healthy subjects are suggested…."

p. 6-17, lines 25-26 I would revise this sentence as follows: "…these diseases are manifestations of a similar disease process."

p. 6-18, line 21 Delete "either" from this sentence.

p. 6-18, line 31 Major factual error. It was the rhinitic subjects in the Holz et al. study, not the asthmatics, that required the higher dose of allergen.

p. 6-26, line 25 The David et al. study cited here does not support the statement that genetic polymorphisms in antioxidant enzymes may modulate responses to ozone and should be deleted. The two studies that first provided evidence in humans for this concept should be added (Bergamaschi et al, 2001 and Corradi et al., 2002).

p. 6-26, line 27 I would revise the second sentence on this line as follows: "It has been suggested that…."

p. 6-26, lines 29-30 I would revise this sentence as follows: "Interindividual variability in O3 responsiveness (FEV1) changes) may be related…."

p. 6-27, lines 1-2 I would revise this sentence as follows: "Adults with GSTM1null only genotype did not show increased responses to O3."

p. 6-27, line 4 Spell out exhaled breath condensate.

p. 6-27, line 27 I would revise this sentence as follows:"…between susceptibility and specific polymorphisms."

p. 6-31, line 9 Should be "inherent variability… makes their assessment difficult."

p. 6-32, line 6 I would revise this sentence as follows: "…did not promote the early-phase nasal response to allergen."

p. 6-32, lines 21-24 I would revise this sentence as follows: "…suggest that these cell types release mediators found in the BALF of O3-exposed humans." I strongly disagree with minimizing the role of alveolar macrophages in the airway responses to ozone.

p. 6-33, lines 10-12 I would revise this sentence as follows: "However, IL-8 can still remain elevated at 18 h post-O3 (4 h at 0.2 ppm O3 versus FA) in healthy subjects (Balmes et al., 1996)." It is confusing to discuss the response of asthmatic subjects here. This paragraph deals with healthy subjects. The next paragraph deals with asthmatics.

p. 6-33, lines 16-18 I would revise this sentence as follows: "In addition to the influx of PMNs, lymphocyte numbers…."

p. 6-35, line 3 Delete "the" before epithelial expression in this sentence.

p. 6-35, lines 5-8 I would revise this sentence as follows: "Using data from the same experiment, Stenfors and colleagues (2002) were unable to detect a difference in the ozone-induced increases in neutrophil numbers between the 15 mild asthmatic and 15 healthy subjects…."

p. 6-36, line 5 Should be NQO1.

p. 6-36, line 6 I would substitute "antioxidant" for "redox" here.

p. 6-36, line 27 Delete BAL protein from this line. Total protein in the next sentence usually refers to BAL protein so the two sentences are contradictory as written. It is my recollection of this paper that total protein in BAL did not become attenuated after 5 days of exposure.

p. 6-37, lines 7 and 12 Use BALF instead of BAL.

p. 6-38, lines 12-13 This sentence is contradicted by the following paragraph. I would delete it.

p. 6-39, lines 6, 14, 24, and 27 Use BALF instead of BAL.

p. 6-40, section 6.10 This section should include a brief description of the Corradi et al., 2002 paper which reported increased 8-OhdG in peripheral blood lymphocytes after ozone exposure.

6-42, line 9 Should be at-risk "individuals."

John Balmes: Review of Chapter 8

GENERAL COMMENTS: Overall, this integrative synthesis does a reasonable job of capturing the major elements from Chapters 4-6 that are relevant to the review of the current primary NAAQS for ozone. One concern is that the chapter is very long – 87 pages of text. This length is not necessary to the purpose of providing an integrative synthesis of ozone exposure and health effects. In fact, the excessive length could be considered detrimental to this purpose. The length of the chapter could be trimmed if less detail about specific studies were provided. Such detail is available in Chapters 4-6 and should not be repeated here. While the provision of the conclusions of the 1996 Ozone AQCD is valuable to remind readers of the historical record, this section could be shortened by summarizing rather than quoting verbatim.

While the goal of trying to integrate results from both experimental and epidemiological studies into coherent concepts about how ozone mechanistically induces health effects is important, integration should not be forced when the data are inadequate. In my view, this is the case with regard to the potential mechanisms of the cardiovascular morbidity and mortality effects that may be associated with exposure to ambient ozone. For example, the mild effect on arterial oxygen tension observed by Gong et al. is overemphasized as a likely cause of myocardial ischemia among the general population. In my judgment, the state of knowledge about the potential mechanisms of ozone-related cardiovascular toxicity is insufficient to support the results of epidemiological studies that have linked ambient ozone to cardiovascular morbidity and mortality.

Another concern involves the repeated statement that "the current body of evidence remains inconclusive regarding ambient O3 effects on risk of emergency department visits." While this my be true for ED visits for all conditions, the consistency of results of multiple epidemiological

studies of ED visits for asthma should be highlighted in the chapter. Figure 8-5A shows that 10 of 11 studies showed an increase in ED visits for asthma with nine achieving statistical significance.

SPECIFIC COMMENTS

p. 8-4, line 6 Spell out MSA when first used.

p. 8-19, line 14 Confounders should not be an issue with experimental studies. There can be problems with the experimental design, but these are not properly speaking confounders.

p. 8-20, line 8 I would revise this line as follows: "endocrine and neuronal factors)…."

p. 8-21, lines 27-30 I would revise this sentence as follows: "Only when the resting rats were exposed to 2 ppm O3 for 2 h were the $^{18}O_3$ labeling of BALF constituents and indices of effect (i.e., BAL cells and protein at 24 h) comparable with those of exercising humans…."

p. 8-23, line 11 I would add the following to this line: "…in developing lung tissue and different compartments of the adult respiratory tract, can be…."

p. 8-23, line 27 I would delete "tracheobronchial" from this line.

p. 8-28, lines 8-10 I would revise this sentence as follows: "Though these controlled human exposure studies may have limited statistical power (due to the lower number of subjects compared to panel or field studies)."

p. 8-29, line 11 For consistency, I would use airway "responsiveness" rather than "reactivity."

p. 8-31, lines 6-7 The term "chronic degenerative lung disease' is not one generally used in the medical and scientific literature. I suggest substituting "non-reversible structural damage to the lung."

p. 8-31, line 8 I would revise this line as follows: "…greater injury observed in monkey lung…."

p. 8-32, line 14 Would delete "membrane" from this line.

p. 8-33, lines 12-15 I would revise this sentence as follows: "Mean changes in inflammatory markers…included marked individual differences;…"

p. 8-33, line 21 I would add "for acute inflammation" after "threshold dose."

p. 8-34, line 5 For consistency, I would substitute "BALF" for "BAL fluid".

p. 8-35, lines 8-11 The difference between BAL protein and total protein in BAL escapes me. I recall this paper as showing no attenuation of total protein in BAL so I would delete "BAL protein" from line 10.

p. 8-35, lines 20-22 I would start this sentence as follows: "A few other studies…."

p. 8-36, line 4 I would revise this line as follows: "…and possible airway remodeling is not known."

p. 8-37, line 8 Add "the" before 1996 in this line.

p. 8-37, line 13 Spell out ELF when first used.

p. 8-38, line 1 For consistency, substitute "airway" for "bronchial" here.

p. 8-38, line 26 I would revise this line as follows:"…factor (PAF) in the O3-induced inflammatory response.

p. 8-39, lines 36-37 I would revise this line as follows: "…(2) *robustness* of reported associations to sensitivity analyses to assess the effect of meteorological factors, temporal trends, copollutant exposures, measurement error, etc.;.…"

p. 8-57, line 30 Should be "analyses… are rather limited."

p. 8-57, lines 30-31 through p. 8-58, lines 1-2 I would revise this line as follows: "Analysis of the data from chronic ozone exposure studies indicate possible associations between O3 and changes in lung function; but, overall, the strength of the evidence does not allow establishment of a likely relationship between chronic O3 exposure and increased respiratory morbidity and mortality."

p. 8-58, line 24 Would delete "the two major health endpoints" from this sentence because "morbidity and mortality" are overly broad categories to be characterized as health endpoints.

p. 8-58, lines 29-31 This sentence is poorly written. I would revise this line as follows: "The discussion in each subsection summarizes pertinent key information and then presents the biological plausibility based on toxicological studies of effects attributed to ozone exposure in epidemiological studies."

p. 8-60, Table 8-1 To my knowledge, FEV1 cannot be measured in animals.

p. 8-62, Fig. 8-10 Would delete "epithelial" from title of figure because alveolar macrophages and other inflammatory cells contribute to the release of mediators.

p. 8-62, lines 1-3 Would substitute "other mammalian" for "animal" and add "these" before the final "species" here.

p. 8-63, line 28 I would revise this line as follows: "…(h) individual sensitivity factors such as age…."

p. 8-64, line 30 For consistency, would substitute "airway" for "bronchial" here.

p. 8-65, line 19 Would substitute "results" for "resulting."

p. 8-65, line 20 I would revise this line as follows: "Analysis of BALF for plasma influx markers…."

p. 8-65, lines 30-31 through p. 8-66, line 1 These are likely to be due to a large extent to genetic factors, but as yet these factors remain largely unidentified. Personal characteristics such as age, smoking history, and allergies may also be contributing factors to intersubject variability, with age being particularly important.

p. 8-66, lines 1-5 I would delete these lines.
p. 8-66, line 15 I would revise this line as follows: "…indicated a possible mechanism for ozone effects on atherosclerosis."

p. 8-67, line 12 I would revise this line as follows: "…enhanced responsiveness to acute O3 exposure in terms of pulmonary function changes compared to healthy subjects."

p. 8-67, line 21 I would revise this line as follows: "Increased incidence and duration of O3-induced nonspecific airway responsiveness could have…."

p. 8-68, line 14 I would revise this line as follows: "The hemodynamic and neurohumoral effects…."

p. 8-68, lines 15-18 I would revise this sentence as follows: "Two observations in human clinical studies: (1) O3-induced impairment in alveolar-arterial oxygen transfer (Gong et al., 1998) and (2) O3-induced ventilation-perfusion mismatch (Foster et al., 1993, 1997) suggest the potential for a cardiovascular impact of O3 exposure on individuals with preexisting cardiopulmonary disease (e.g., ischemic heart disease and COPD).

p. 8-68, lines 18-20 I would delete this sentence.

p. 8-68, line 21 I would revise this line as follows: "Cardiovascular disease conditions and COPD are common among older age groups."

p. 8-68, lines 22-23 I would delete this sentence.

p. 8-68, lines 23-24 I would revise this line as follows: "The recent observations of ozone-induced vasoconstriction in a controlled human exposure study by Brook et al. (2002) suggests another possible mechanism for O3-related exacerbations of preexisting cardiovascular disease.

p. 8-68, lines 26-30 I would delete these lines. The results of these toxicological studies are tangential to the argument made in the previous paragraph.

p. 8-71, line 27 Would revise this line as follows: "copollutant exposures."

p. 8-72, lines 24-30 These sentences should be moved as a new paragraph to line 14 to precede the discussion of human genetic susceptibility studies. I would also revise the first sentence (lines 24-27) as follows: "…evaluated in these animal toxicology experiments.

p. 8-72, line 16 The David et al. study did not look at the effect of antioxidant enzyme genetic polymorphisms on ozone-induced responses and should be deleted here. Two references should be added because these are the first to study the effect of these polymorphisms on such responses, Bergamaschi et al, 2001 and Corradi et al., 2002. In addition, Yang et al., 2005 should be added as the first study to look at inflammatory gene polymorphisms and responses to ozone. I also suggest adding a sentence such as "The lack of correlation between lung function and airway inflammatory responses to ozone in healthy subjects, combined with the evidence of separate chromosomal loci for ozone-induced AHR and airway inflammation in inbred mice, suggests that these two responses are probably separated regulated."

p. 8-72, line 19 Would add "risk of " before O3-induced lung function changes.

p. 8-72, line 31 Would add "animal and human experimental" before studies here.

p. 8-73, lines 15-18 I would revise this sentence as follows: "…with preexisting lung diseases, especially asthma."

p. 8-73, line 18 I would substitute "asthma" for "disease" in this line.

p. 8-73, lines 20-21 I would revise this sentence as follows: "Several available human exposure studies have shown…." Stenfors and coworkers should not be referenced here. These investigators did not find a difference in PMN influx into BALF between healthy and asthmatic subjects.

p. 8-73, line 22 The correct reference here is not Stenfors et al., 2002, but rather Schierhorn et al., 1999.

p. 8-73, lines 30-31 through p. 8-74, lines 1-2 I would revise this line as follows: "In addition, some controlled O3 exposure studies in human subjects with asthma (Hiltermann et al., 1999; Basha et al., 1994; Scannell et al., 1996) reported increased secretion of IL-8, suggesting a mechanism for increased neutrophilic inflammation."

p. 8-74, line 26 I would revise this line as follows: "…in susceptible individuals with preexisting disease being seen as adverse."

p. 8-76, Table 8-2 For consistency, substitute "airway" for "bronchial" responsiveness.

p. 8-77, Table 8-3 For consistency, substitute “airway” for “bronchial” responsiveness.

p. 8-80, line 10 I would revise this line as follows: “changes in heart rate and rhythm.”

p. 8-80, line 15 Should be “Pacific”.

p. 8-82, lines 23-25 This first bullet only notes that panel studies have investigated short-term effects and does not present any important findings. I suggest eliminating this bullet.

p. 8-83, line 25 Delete “on” from this sentence.

p. 8-84, lines 3-4 In my view, this sentence is incorrect regarding ED visits for asthma.

p. 8-84, line 13 I would revise this line as follows: “…changes observed in human and animal toxicology studies are consistent with human epidemiological studies.”

p. 8-84, lines 26-31 Too much detail is given in this bullet.

p. 8-85, lines 1-2 Prior to this sentence, I suggest adding a sentence such as “Another study in which healthy subjects were exposed to a lower concentration of ozone (0.2 ppm) for 4 consecutive days showed similar findings.” Better yet, provide a shorter bullet that mentions both studies. Including both consecutive-day exposure studies that looked at airway injury/inflammation strengthens the point of the bullet.

p. 8-85, lines 25-30 Again, too much experimental detail is included.

p. 8-86, line 8 Would add “status” after “socioeconomic”.

p. 8-87, line 1 Would substitute “young adults” for “adolescents given the most responsive subgroup were those aged 18-25.

p. 8-87, line 11 For consistency, would use airway “responsiveness” rather than “reactivity”.

Dr. Ellis Cowling

Dr. Ellis Cowling
North Carolina State University
December 2, 2005

Review of the Air Quality Criteria Document for Ozone and Related Photochemical Oxidants (Second External Review Draft)

General Comments on the New Organizational Format

As indicated in Lester Grant's transmittal letter of November 23, 2005 for this Second External Review Draft of the Criteria Document for Ozone and Related Photochemical Oxidants, the overarching modification in this Second Draft is restructuring of the three volumes that comprise it. Specifically, beginning each chapter with a summary of key information from previous air quality criteria documents and then giving an interpretive evaluation of newly developed scientific information in the remainder of the chapter.

Charge Questions -- Overall

Does this new format meet Panel members' expectations in terms of facilitating reading and comprehension of the evaluations and conclusions that are communicated in the overall criteria document materials, *i.e.*, in the AQCD's main chapters and accompanying annexes? Or, would alternative sequencing of materials to have a given annex immediately follow its relevant main chapter be more "reader friendly" and effective?

For our individual CASAC-member review purposes it might be a little more convenient to have the annexes attached to the chapter. But we individual CASAC members are not by any means the only users of these Criteria Documents. Many other readers will be very interested in the relationships between emissions of precursors, atmospheric chemistry and physics, air quality and human exposure, toxicology, and epidemiology and ozone and UVB effects on materials, vegetation, and ecosystems. Many readers also will be interested in what has been learned in each of these specific areas o science since the last Criteria Document. Thus, I favor the new format mainly because it has the potential to satisfy a broader array of interested audiences than having main chapters and annexes following each other.

Charge Questions – Executive Summary

What are the Panel's views with regard to the format of the newly-provided Executive Summary and the soundness of its scientific content including consistency of the restatement of key findings and conclusions stated in the main chapters of the document?

I very much favor the inclusion of an overall Executive Summary since it is likely to be the most often used part of the whole Criteria Document. I also believe that most of the text of an effective Executive Summary should take the form of carefully crafted statements of scientific

findings that cover 'the distilled essence of present scientific and technical understanding of the phenomena or processes to which it applies."

I further recommend that all authors, consultants, editors, and managers engaged in preparation of Criteria Documents take full advantage of and use the attached published "*Guidelines for the Formulation of Scientific Findings to be Used for Policy Purposes*." These guidelines, written in the form of checklist questions, were developed by the Oversight Review Board of the National Acid Precipitation Assessment Program (ORB-NAPAP) to assist scientists in formulating statements of research results to be used in policy decision processes.

GUIDELINES FOR THE FORMULATION OF SCIENTIFIC FINDINGS TO BE USED FOR POLICY PURPOSES

The following guidelines in the form of checklist questions were developed by the NAPAP Oversight Review Board to assist scientists in formulating presentations of research results to be used in policy decision processes.

1) **IS THE STATEMENT SOUND?** Have the central issues been clearly identified? Does each statement contain the distilled essence of present scientific and technical understanding of the phenomenon or process to which it applies? Is the statement consistent with all relevant evidence that is available in the published literature. Is the statement contradicted by any important evidence in the published literature? Have apparent contradictions or interpretations of available evidence been considered in formulating the statement of principal findings?

2) **IS THE STATEMENT DIRECTIONAL AND, WHERE APPROPRIATE, QUANTITATIVE?** Does the statement correctly quantify both the direction and magnitude of trends and relationships in the phenomenon or process to which the statement is relevant? When possible, is a range of uncertainty given for each quantitative result? Have various sources of uncertainty been identified and quantified, for example, does the statement include or acknowledge errors in actual measurements, standard errors of estimate, possible biases in the availability of data, extrapolation of results beyond the mathematical, geographical, or temporal relevancy of available information, etc. In short, are there numbers in the statement? Are the numbers correct? Are the numbers relevant to the general meaning of the statement?

3) **IS THE DEGREE OF CERTAINTY OR UNCERTAINTY OF THE STATEMENT INDICATED CLEARLY?** Have appropriate statistical tests been applied to the data used in drawing the conclusion set forth in the statement? If the statement is based on a mathematical or novel conceptual model, has the model or concept been validated? Does the statement describe the model or concept on which it is based and the degree of validity of that model or concept?

4) **IS THE STATEMENT CORRECT WITHOUT QUALIFICATION?** Are there limitations of time, space, or other special circumstances in which the statement is true? If the statement is true only in some circumstances, are these limitations described adequately and briefly?

5) **IS THE STATEMENT CLEAR AND UNAMBIGUOUS?** Are the words and phrases used in the statement understandable by the decision makers of our society? Is the statement free of specialized jargon? Will too many people misunderstand its meaning?

6) **IS THE STATEMENT AS CONCISE AS IT CAN BE MADE WITHOUT RISK OF MISUNDERSTANDING?** Are there any excess words, phrases, or ideas in the statement which are not necessary to communicate the meaning of the statement? Are there so many caveats in the statement that the statement itself is trivial, confusing, or ambiguous?

7) **IS THE STATEMENT FREE OFSCIENTIFIC OR OTHER BIASES OR IMPLICATIONS OF SOCIETAL VALUE JUDGMENTS?** Is the statement free of influence by specific schools of scientific thought? Is the statement also free of words, phrases, or concepts that have political, economic, ideological, religious, moral, or other personal-, agency-, or organization-specific values, overtones, or implications? Does the choice of how the statement is expressed rather than its specific words suggest underlying biases or value judgments? Is the tone impartial and free of special pleading? If societal value judgments have been discussed, have these judgments been identified as such and described both clearly and objectively?

8) **HAVE SOCIETAL IMPLICATIONS BEEN DESCRIBED OBJECTIVELY?** Consideration of alternative courses of action and their consequences inherently involves judgments of their feasibility and the importance of effects. For this reason, it is important to ask if a reasonable range of alternative policies or courses of action have been evaluated? Have societal implications of alternative courses of action been stated in the following general form?:

"If this [particular option] were adopted then that [particular outcome] would be expected."

9) **HAVE THE PROFESSIONAL BIASES OF AUTHORS AND REVIEWERS BEEN DESCRIBED OPENLY?** Acknowledgment of potential sources of bias is important so that readers can judge for themselves the credibility of reports and assessments.

Specific Comments on the New Organizational Format

This new organizational format for the organization of the relatively brief Main Chapters of the Criteria Document itself, and the more detailed Annexes, is a very good idea. It is also a very good idea to have an Executive Summary for the whole Criteria Document – one that summarizes key scientific findings and that emphasizes new developments since the last Criteria Document. Finally, it is also a very good idea to continue the practice of providing detailed annexes that provide even more thorough analyses and interpretations of the large body of scientific information on which each Main Chapter is based.

These two innovations in the overarching method of organization of this Criteria Document will better serve the interests of the wide variety of audiences that are interested to learn more about scientific understanding of ozone and related photochemical oxidants and their effects on both human health and welfare. Thus, I believe these two revisions in organizational structure should be retained not only in the Final Draft of this Criteria Document dealing with ozone and related photochemical oxidants but also should be used in preparing Criteria Documents for other Criteria Pollutants.

In doing so, it is of course important that the different target audiences for the Executive Summary, the Main Chapters of the Criteria Document itself, and the various Annexes be very well defined and well understood by the staff and consultants that prepare these three different treatments of the same body of scientific knowledge.

In doing so, it is even more imperative that the scientific content and objectivity of the Executive Summary be consistent not only with the scientific content and objectivity of the main chapters of the Criteria Document itself, but also with the scientific content and objectivity of the more detailed Annexes. Differences in the content of these three distinct parts should be based almost exclusively on their importance to their respective target audiences. But discrepancies in either scientific content and/or objectivity of these three distinct parts of the Criteria Document will inevitably lead to decreased confidence in the validity and reliability of all three parts. Thus such discrepancies must be carefully avoided. This will require a larger degree of common

understanding among authors, consultants, editors, and managers of the criteria document development process than I believe has been achieved to date.

One specific suggestion for avoiding discrepancies in communication among Executive Summaries, Main Chapters, and more detailed Annexes is to require that the very same carefully-crafted summary statements of scientific findings are not only included (but also printed in bold-face type) within <u>all three parts</u> of complex scientific assessment documents. This editorial device is used in many high-quality National Research Council assessment reports that also deal with very complex policy relevant scientific issues.

Comparison of the Science Content and Objectivity of Main Chapter, Annex, and Executive Summary for Chapter 9 "Environmental Effects: Ozone Effects on Vegetation and Ecosystems."

As I thought was appropriate to my role as an experienced plant physiologist and ecologist with a keen interest and substantial experience in producing carefully crafted statements of policy-relevant scientific findings, my review of the vegetation and ecosystem effects of ozone in this Second Draft Criteria Document was done in three progressive stages:

1) Review of the 410 pages of "Annex AX9 – "Environmental Effects: Ozone Effects of Vegetation and Ecosystems;"
2) Review of the 27 page Main Chapter 9– "Environmental Effects: Effects of Ozone on Vegetation and Ecosystems;"
3) Review of the 4 pages within the Executive Summary dealing with – "Vegetation and Ecological Effects" (pages E-27 through E-32).

The Annex for Chapter 9 contains a very thorough and well-balanced summary of existing knowledge regarding the effects of ozone on crops, forests, and natural ecosystems. When comparisons were made between the scientific understanding obtained from the Annex and the Main Chapter, however, I was much less satisfied with both the content and objectivity of the Main Chapter than of the Annex. Further more, when comparisons were made between the qualities of understanding obtained from the statements of scientific findings in the Executive Summary, still other important discrepancies of both content and objectivity were found. In fact, my confidence in the vegetation and ecosystem effects parts of the Criteria Document was partially restored during my review of the scientific content of the Executive Summary. But my concern about the objectivity of the information presented in the Executive Summary remained as discussed more fully below.

Charge Questions – Chapter 9

What are the CASAC ozone Panel's views on the adequacy of the much shorter evaluative discussion now comprising Chapter 9 of the 2nd Draft Ozone OQCD? Have any crucially important new FACE studies or other crucially important types of ecological effects studies been missed. Are there additional modifications to the main body of Chapter 9 or accompanying annex materials that would further strengthen the overall coverage and interpretation of findings related to ozone vegetation/ecosystem effects?

As discussed below, the most important suggestions I would make for improving Chapter 9 and its relevancy to the scientific bases for secondary ozone NAAQS is to eliminate all discrepancies in both the scientific content and the objectivity of the presentation of current

knowledge with regard to exposure indices in the Annex, the Main Chapter, and the Executive summary. All three parts of this Criteria Document are dealing with the same body of scientific knowledge. Thus all three parts of the document should tell the same scientific story!

Comparison of the Science Content and Objectivity of Criteria Document Discussions regarding the Value and Usefulness of Exposure Indices

As indicated in my written comments to CASAC dated March 21, 1996 and quoted again in my written comments on April 29, 2005, for some years now, I have been convinced that the scientific evidence available as early as 1995 regarding ozone effects on crops, forests, and natural ecosystems was sufficient to justify serious consideration of a secondary standard for ozone different in form from the primary standard. This same conviction was further supported in my April 2005 review of the First External Review Draft of this Ozone Criteria Document and also by written comments dated October 20, 2005 on the "Ozone Environmental Assessment Plan: Scope and Methods for Exposure, Risk, and Benefit Assessment."

After reviewing this latter document, what a delight it was to respond with the following written comments:

> "One of the most interesting parts of the August 17, 2005 "Ozone Environmental Assessment Plan" is the following statement which outlines more thoroughly than I have ever seen before, the details of how the Administrator of EPA **did in fact propose in 1997** to "replace the existing 1-hr O_3 secondary [welfare based] NAAQS with … a new seasonal standard expressed as a sum of hourly concentrations greater than or equal to 0.06 ppm, cumulated over 12 hours per day during the maximum 3-month period during the O_3 monitoring season (SUM06), set at a level of 25 ppm-hr … or alternatively … a [secondary] standard identical to the proposed 0.08 ppm, 8-hr primary [public health based] standard."
>
> "In her final decision, the Administrator … decided that it was not appropriate **at that time** [emphasis by me] to establish a new separate seasonal secondary standard … [but that] setting the secondary standard equal to the primary standard would allow EPA the opportunity to evaluate more specifically the improvement in rural air quality and in O_3–related vegetation effects resulting from measures designed to attain the new primary standard. This information would allow for better evaluation of the incremental need for a distinct seasonal secondary standard in the next review of the O_3 criteria and standards (62 FR 38877-78, July 18, 1997)."

> "Based on the scientific evidence contained in the [First External draft of the] 2005 Criteria Document for Ozone, and the approaches outlined in the present Ozone Environmental Assessment Plan, I am even more convinced that **EPA Staff should do all within their powers of persuasion (after further analysis of more currently available scientific evidence as proposed in this Plan!) to persuade the Administrator of EPA that a secondary (public welfare-based) standard for ozone different in form from the primary standard should be promulgated and implemented by the Agency in 2007**."

I am also aware that EPA's adoption in 1997 of an 8-hour standard with a maximum allowable ozone concentration of 80 ppb is giving somewhat greater (but still not adequate) protection of crops, forests and natural ecosystems than the standard with a maximum 1-hour ozone concentration of 120 ppb.

With these written statements and further awareness of the differences between the 1-hour and 8-hour standards in mind, I was very much heartened by the additional evidence presented in Annex AX9 of this Second External Review Draft. Clearly an additional body of evidence has been accumulated in recent years that provide further support for a decision by EPA's OAQPS Staff to present an even persuasive case to the Administrator of EPA for consideration and promulgation in 2006 or 2007 of a Secondary Ozone Standard different in form from the 8-hour primary standard.

This heartened perspective in reviewing the AX9 Annex, however, was considerably shaken when I reviewed the Main Chapter (Chapter 9) on "Ozone Effects on Vegetation and Ecosystems" in the Second External Draft of the Ozone Criteria Document. Although some parts of this chapter were generally consistent in content and objectivity with the content and objectivity of the Annex, this was not true especially in comparing the evidence presented in Section 9.5 on "Effects-Based Air Quality Exposure Indices" in the Main Chapter (pages 9-11 through 9-13) with those of Section AX9.4 "Effects-Based Air Quality Exposure Indices" (pages AX9-196 through AX9-224).

It is not surprising that the total number of references dealing with exposure indices is much smaller in the Main Chapter than in the comparable sections of Annex 9. But it is very surprising (and disappointing) that much less attention is given in the Main Chapter to European literature in general and especially to comparison of the European AOT40 index and the alternative Sum06. Sum 08, and W-126 indices most often studied and discussed here in the US. There also is a notable difference in the frequency and tone of negative or very cautionary statements about the value and reliability of these several possible exposure indices in the Main Chapter compared to the less frequent negative comments and the generally more positive tone in the comparable Annex discussions of the same body of science.

Final Concluding Remarks

As suggested earlier in these written comments, one specific suggestion for avoiding discrepancies in communication among Executive Summaries, Main Chapters, and more detailed Annexes is to require that the very same carefully-crafted summary statements of scientific findings are not only included (but are also printed in bold-face type) in <u>all three parts</u> of complex scientific assessment documents. This editorial device is used in many high-quality National Research Council assessment reports that also deal with very complex policy relevant scientific issues.

Dr. James D. Crapo

December 2005
Critique of Second Draft Air Quality Criteria Document for Ozone
James Crapo

Overall, the Second Draft Ozone AQCD is substantially improved and provides an excellent summary of the chemistry, exposure patterns, dosimetry, toxicology, and epidemiologic aspects of ozone exposure. My comments will focus on Chapters 7 and 8. The primary purpose of this document is to provide the scientific foundations for considering the form and level of the air quality standard for ozone. An abundant literature over the past 50 years has clearly demonstrated the potential toxicologic effects of high level exposures to ozone. Thus, the primary focus of this AQCD ultimately needs to be on our evolving knowledge of exposures and potential adverse health effects occurring near or below the current air quality standard for ozone.

Chapter 7 (Epidemiologic Studies of Human Health Effects Associated with Ambient Ozone Exposure)

This chapter does an overall excellent job of summarizing human epidemiology (including field studies, panel studies and ER and hospitalization utilization) of health effects associated with ozone exposure. An issue that needs to be addressed for clarity in this chapter is inclusion of the critical data on each study needed to assess its impact and applicability to low ambient ozone exposure. A number of the studies are presented in a form that does not allow correlation with the level of ozone exposure involved without requiring the reader to return to the primary data or Chapter 7 of the Annex. For example, some studies are reported with only an odds ratio for a change in function relative to a 30-40 ppb increase in ozone exposure without defining the range of ozone exposures over which data was collected and, thus, its relevance to common ambient levels. For each table, figure, or reported study, the range of ozone levels involved should be given in this chapter (as opposed to requiring use of the Annex).

Section 7.6.8, the summary of key findings and conclusions, should be revised so that each of the 14 points are correlated to the ozone exposure levels to which the conclusions apply.

Chapter 8 (Integrative Synthesis: Exposure and Health Effects)

Chapter 8 would benefit from being shortened and more focused on the issue of the application of data and conclusions to health effects relevant to ozone exposure levels near or below the current ozone air quality standard. For a substantial portion of the current chapter, it is unclear as to whether the data used to show ozone related adverse health effects come from relatively high ozone exposures or from exposures near or below the current air quality standard. This chapter does not need to focus on toxicologic or health effects of ozone at levels substantially higher than the current air quality standard.

I would recommend creating a table listing all studies that demonstrate possible adverse health effects occurring at or below the current air quality standard. Following this table there should be a discussion of the strengths and weaknesses of each of the studies. The weight or importance of each of these studies with respect to overall interpretive values should also be discussed. This is essential to allow the reader to correctly integrate the value of the studies and potential biases that could be involved. The role of bias in influencing both the outcome and the reporting of positive studies needs to be more thoroughly considered. This is particularly true since the air quality standards are beginning to approach the policy relevant background levels for ozone. Thus, subtle bias could have substantial impact. I would recommend a second table that lists studies showing no adverse health effects at exposure levels at or below the current ozone air quality standard. Again, the strengths and weaknesses of these studies should be clearly identified. It is important that this chapter does not contain an inappropriate bias emphasizing positive studies over equally well designed studies that have a negative result in terms of adverse health effects.

Section 8.7, summary and conclusions, needs to be revised. The bullets need to identify the relevance of the reported studies or conclusions to ozone exposure levels at or below the current air quality standard. Each bullet should contain information regarding the relevance of that conclusion to ozone levels at or below the current air quality standard. Finally, conclusions regarding data that address the form of the standard should be included in this section.

Dr. William (Jim) Gauderman

Ozone AQCD Draft 2
Jim Gauderman

Chapter 7

Section 7.5.4: Gauderman et al. (2002) reported results for several two-pollutant models in analysis of both FEV1 and MMEF growth in the second cohort of the CHS (Tables 4 and 5 of that paper). For both lung function outcomes, the only two-pollutant model in which both pollutants were statistically significant included O_3 and NO_2. This suggests a possible joint effect of these two pollutants on lung function development. However, while it is worth pointing out the ozone associations in the second cohort, the overall evidence based on both cohorts of the CHS demonstrates stronger associations with non-ozone pollutants than with ozone.

Page 7-51, line 21: The effect estimates presented here do not agree with those shown in the annex, table AX7-1. This may be simply because the former are scaled to 30 ppb while the latter are scaled to 20 ppb, but I can't get one from the other. Suggest using the same scaling factor to avoid confusion.

Dr. Henry Gong

Individual Review Comments for U.S. EPA Ozone AQCD (2nd draft).
Henry Gong, Jr., M.D., 11/21/05
CASAC Ozone Review Panel

I am focusing primarily conceptual comments for this pre-conference review on Chapter 6, Annex AX6, Chapter 7, and Chapter 8 (2nd Draft of Ozone AQCD).

Chapter 6 and ANNEX AX6, "Controlled Human Exposure Studies of Ozone and Related Photochemical Oxidants"

General Comments

The comprehensive and logical chapter reads well and has been improved, as compared to the First Draft. The Staff authors have generally responded to most of my April/May queries in satisfactory manner. Overall, the chapter represents a useful and accurate scientific update and summary, as does the Annex AX6. As such, I have fewer comments than compared to my queries in April/May, 2005.

Specific Comments

1. Page 6-7/lines 1-2: "ozone uptake" is first used here. Can you succinctly define the term for the reader? The term is well described on AX6-9.
2. Pages 6-15, 6-20, and 6-22: The references to the paper by Hoppe (Int J Hyg Environ Health 2003;206:505-516) are inserted to essentially support the concept that asthmatics respond differently to ozone exposure. However, this reference is not cited in Annex AX6, although it is prominently used in Chapter 7 (Epidemiology). I am not convinced that this paper belongs in Chapter 6 for the following reasons (which unfortunately may appear to be a post-publication critique of the paper): (a) the different groups have different ages and ventilation rates; (b) the ozone exposures are likely very different among the groups and different from those used in controlled clinical studies (i.e., only ozone in filtered air); (c) temperature appears to be strong confounder with ozone and it is unclear if any statistical method can disentangle ozone and temperature effects in their data; (d) ozone effects on lung function occur within 1-2 hours after initiation of chamber exposure but peaks the day following exposure in the epidemiological study, suggesting that the observed phenomena are different (or the time of measurements differ). Thus, I recommend deleting this paper from Chapter 6.
3. Page 6-33/line 1: "health" should be "healthy."
4. Page 6-34/Figure 6-4: Excellent figure with important concepts. The shaded blocks presumably represent 12-hour "progression" periods. If so, then the shaded areas may be misleading since some responses appear to progress beyond 12 hours, whereas others appear to begin to resolve in much less than 12 hours. Perhaps this is only an issue about what the shaded blocks represent in the figure?
5. AX6-2/line 30: "..repeatedly…" sounds better.
6. AX6-5 and AX6-107 (Table): The paper by Blomberg A et al. (Clara cell protein as a biomarker for ozone-induced lung injury in humans. Eur Resp J 2003;22:83-88) is not referred to in Chapter 6 and is understated in ANNEX AX6. Yet, I believe that this paper is

a noteworthy contribution in that it shows the presence (increase) of a lung protein in blood, reflecting increased epithelial permeability. There are, to date, no other easily measured, noninvasive biomarkers such as this one, to my knowledge. Thus, the Clara cell protein should be given more credit as a promising biomarker for increased epithelial permeability (in this case, for ozone-induced injury); added to the permeability sections of Chapter 6 and ANNEX AX6; and perhaps attributed to in the pathogenesis of cardiovascular alterations (e.g., interstitial and pulmonary edema, with or without congestive heart failure) in Chapters 6 and 7.

7. Page AX6-70/lines 14-31: The entire paragraph on budesonide inhalation (Nightingale et al, 2000) is not appropriate here since the section speaks to genetic factors for ozone responses. This point of the study is adequately covered on AX6-123.
8. Page AX6-93/line 28-30: You could also interpret the findings on exercise-induced bronchoconstriction to indicate that "realistic" doses of ozone do not generally exacerbate exercise-induced asthma.

Chapter 7

Chapter 7 is well written and is very "educational" for me. I finally understand some difficult concepts much better now. Thus, the Chapter represents a very comprehensive and explanatory summary of epidemiological papers.

Comments

1. Ozone Mortality: I do not understand the calculation and relevance of "per standardized increment" of ambient ozone that is frequently used in related figures and text (e.g., Figure 7-20). The reader is referred to "Section 7.1.3.2 Ozone Exposure Indices Used," presumably for an explanation, but I must admit that the text is not elucidating to me. Staff may wish to counsel me! However, can the text be re-phrased with instructive examples?
2. Page 7-101/line 22: Gauderman is mis-typed.
3. Page 7-104/lines 19-27: The concluding statement about findings from Gong et al (1998b) is satisfactory but the lack of ozone response in a chamber may also be related to an aging effect.
4. The paper by Hoppe et al (2003) is appropriately referred to several times in Chapter 7. Please see my comments about this paper in Chapter 6 (above).
5. Page 7-151/line 40-42: The effect of aging on lung function responses to ozone appears understated epidemiologically and "ignores" ample data from clinical studies about age.

Chapter 8

Chapter 8 is generally well written, informative, and an excellent distillations of the previous chapters, including the 1996 Ozone AQCD. The Chapter generally contains accurate syntheses and does not lose any key information (except for some items below).

1. Pages 8-32, 8-33, 8-66, and Table 8-1: Increased epithelial permeability is an important characteristic of ozone-induced injury and is indicated at least four times in this chapter. Thus, I am again surprised that the paper (Blomberg A et al, 2003) on Clara cell protein is not cited. (See my comments in Chapter 6 above)
2. Page 8-85/Section 3: There is no discussion about the epidemiological findings of chronic ozone exposure. Is Staff (lines 11-12) implying that there are none?

Dr. Paul J. Hanson

Comments on the 2nd Draft of the Ozone Air Quality Criteria Document (AQCD), Emphasizing Chapters 9 and 10 and The Related Executive Summary Comments

Submitted by: Paul J. Hanson
Date: December 5, 2005

The EPA staff and expert consultants have done an excellent job incorporating suggestions made by CASAC, the 2nd Draft CD, and the executive summary's use of concise bullets characterizing key findings and conclusions from the main chapters strengthens the document.

Comments on the Executive Summary Bullets:

Page E-7 lines 26 and 27: When I view Figures 3-17 and 3-18 I do not see strong evidence for an increase in O_3 concentrations for the lower end of the measured concentrations. Is this trend fully justified and documented in the peer-reviewed literature? This same question applies to the statement made on page 3-33 lines 25 and 26.

Page E-8 lines 1 and 2: A better statement justifying/explaining this point is provided on page 3-47 lines 7 to 9. Shouldn't the importance of long-range ozone transport be emphasized in the executive summary?

Page E-9 lines 4 to 9: This bullet needs to be reworked. I'm uncertain what the take-home message is supposed to be.

Page E-30 line 21: I would change the word "best" to 'most viable' or 'most practicable'. Much of the discussion in Chapter 9 argues that models of internal O_3 uptake would be the best approach for predicting plant response to O_3 concentrations in the atmosphere.

Page E-30 line 31: Quality of what?

Page E-31 line 6: Within the *Populus* genera sensitivity to ozone varies widely. I would reword this line as: "sensitive clones or genotypes of the *Populus* genera and …."

Page E-31 line 12: Should this be written "…season may underestimate growth effects…"?

Page E-33: It was my understanding that one goal of Chapter 10 was to provide information on how tropospheric ozone influences the ground-level flux of solar ultraviolet radiation leading to alternative human exposures. The information summarized on page E-33 tends to focus on UV-B effects and measurement issues and doesn't really answer the question of interest. A few specific suggestions:

Lines 4 to 8: This bullet might be reworded to state simply that monitoring of surface level UV-B is inadequate to adequately address conclusions regarding connections between tropospheric ozone occurrence and UV-B exposure.

Lines 10 to 16: This bullet is not essential to the executive summary.

Lines 26 to 31: This bullet needs to be expanded to make it a complete statement in the context of tropospheric ozone.

Comments on Chapter 9:

I appreciate the dramatic changes made to the organization of Chapter 9. I found Chapter 9 to be an appropriate statement of the available information on the direct impacts of tropospheric ozone on terrestrial vegetation. The following comments provide additional suggestions that the authors should consider in preparing the final draft.

Several key figures might be brought forward from the Annex for Chapter 9 to provide the reader with visual reinforcement of some of the points being made.

In an attempt to provide a concise general summary, many statements within Chapter 9 have lost the citations to which they may have originally been attributed. The authors should scrutinize the text and provide references to key statements when appropriate.

Page 9-1 line 25: Who's research is being referred to by the phrase "The research"?

Page 9-6 lines 10 and 11: This sentence does not make sense.

Page 9-12 lines 7 and 8: This sentence seemed at odds with the conclusions from Chapter 3 that seemed to state that mean mid-range concentrations were quite stable over this time period.

Page 9-12 lines 18 and 19: This statement should be included in the executive summary in some form.

Page 9-14 line 20: Should this be Table A9-16?

Page 9-14 lines 31 to 33: I would remove this statement. It seems more appropriate to the discussion within the Staff paper. The selection of a 'critical level" is a policy decision.

Page 9-15 lines 23 to 25: For the same reason I would remove this statement.

Page 9-16 line 5: Within the *Populus* genera sensitivity to ozone varies widely. I would reword this line as: "sensitive clones or genotypes of the *Populus* genera and …."

Page 9-16 lines 8 to 13: Citations for these statements are needed.

Page 9-16 lines 14 and 15: Are data on the interactions between interspecific competition and ozone effects available for large trees? I'm not certain this statement can be made at this time even though the hypothesis might be valid.

Page 9-16 lines 17 19: This statement should be reworded to avoid talking about a defined AOT40 value for a specific level of protection (a policy issue). Alternatively, the statement might indicate the level of response associated with given levels of exposure.

Page 9-16 lines 25 and 26: Is there a reference for this statement, and the statements on the top of the next page?

Sections 9.7 and 9.8 are well written, interesting and I agree with the content, however, the authors need to look closely at the language to ensure that hypothesized processes are not presented as factual without adequate support in the peer-reviewed literature.

Page 9-17 line 17: I suggest changing "may even" to 'has the potential too'.

Page 9-17 line 18: I suggest changing "probable" to 'possible'.

Page 9-19 lines 1 and 2: Is the point of this statement that mechanistic models of stomatal response to ozone are not available?

Page 9-19 lines 5 to 7: Some data addressing this point are available from the Aspen and soybean FACE studies.

Comments on Chapter 10: I found this chapter to be well written and easy to follow. The text provides extensive, but I believe appropriate details on the mechanisms of ultraviolet radiation effects on humans and the mechanisms of greenhouse gas forcing associated with climatic change. This background information is needed to prepare the reader for a discussion of the influence of tropospheric ozone on ground-level UV-B exposures and tropospheric ozone's contribution to global greenhouse forcing. As I understand the conclusions, insufficient data and/or analytical capabilities are available at this time to allow exact assessments of the influence of tropospheric ozone on either process.

Page 10-11: The figure is lacking x- and y-axis labels.

Page 10-35 lines 15 and 16: This succinct statement should be used in the executive summary.

Minor Comments;

Page 1-11 lines 11 and 12: Should "September 2005" be 'November 2005'?

Page 3-32 Caption to Figure 3-15: "200" should be '2000'.

Page 3-37 line 13: Would it be more descriptive to change "not reflected these changes" to 'remained nearly constant over time'?

Dr. Jack Harkema

Date: November 30, 2005

Subject: Comments on 1) the 2nd Draft of the Ozone Air Quality Criteria Document (AQCD), with emphasis on Chapter 5, and 2) 1st Draft Ozone Staff Paper (Chapter 3: Policy-Relevant Assessment of Health Effects Evidence)

From: Jack Harkema

1) 2nd Draft of Ozone AQCD
General Comments: The EPA staff and expert consultants to the NCEA-RTP have done an excellent job with this revision and incorporating into the 2nd Draft the comments and suggestions made by the CASAC review panel in May, 2005. The restructuring of the three volumes, focusing the main criteria document chapters on shorter interpretative evaluations of the recent literature, and placing more-detailed descriptive information in the annexes are good improvements and make the document more clear, concise and workable for the reader. The addition of the executive summary with the use of concise bullets characterizing key findings and conclusions from the main chapters also strengthens the document.

Comments on Chapter 5: I found this chapter well written and adequately researched. The chapter is well organized and provides enough detail of pertinent reported research since the last AQCD. The added figures clearly enhance the written text, but more descriptive figure legends are needed. The summaries and interpretations provided at the end of each subsection are also well done and informative. I have listed below a few specific suggestions, questions and minor editorial changes for the authors to consider.

In the introductory paragraphs of each of the subsections, it would be helpful to the reader and give added strength to the document if a few references are provided in the text for some of the key findings that are highlighted.

Page 5-4; lines 9-11 Sentence stating with *Further experiments* . . . needs to be revised to correct grammatical errors and redundancy.

Page 5-5; section 5.2.1.3 This is a good example were a few key references should be provided in the introductory paragraphs.

Figure 5-2 Abbreviations used in the figure should be defined in the legend. Do the highlighted components of *Lung Lining Fluid* always lie below the mucous layer as illustrated? Maybe this could be redrawn to more adequately reflect the text.

5-7; line 24 change *the model* to *this in vitro model*

Figures 5-2 and 5-3 have some redundancy. Maybe one figure incorporating the key information of both would suffice.

5-17; line 19 Is MLN defined? Check.
5-12; Information in lines 1 and 2 are repeated in lines 12 and 13. Delete the introductory sentence in 5.2.3.1 (lines 12 and 13).

5.2.3.2 This section nicely emphasizes the relative influence of C x T for ozone, but a few comments on episodic versus continuous regimens of exposure would also be helpful.

5-26; line 31 end of sentence. Not sure what is meant by *basal lung epithelial permeability*. Clarify.

5-27; line 31 I don't think it is correct that only ozone exposures ≥ 1 ppm induce mediators to recruit PMNs in the airways of exposed laboratory animals. For example, it has been reported that monkeys exposed to 0.15 ppm ozone for 6 days had neutrophilic rhinitis (Harkema et al. Am J Pathol. 1987 Jul;128:29-44). Be careful in your wording not to over generalize especially in reference to specific exposure concentrations and responses in laboratory animals.

5-36; line 25 Provide the strain of mice used.

5-38; line 19 Not sure where the . . . *0.15 ppm in rats and lower concentrations in primates* comes from. Check.

5.2.4.3 It may be helpful to add the figure by Dungworth illustrating tissue response and length of exposure (as found in the previous AQCD) to this document to complement the first paragraph of this section.

5-42; line 27 Add epithelial hyperplasia to the list of effects on nasal mucosa.

5-42; line 29 Fibrotic changes should refer to lung tissue.

The subsections on coexposures are nicely done.

5-77; line 23 Delete *of*.

2) 1st Draft Ozone Staff Paper (Chapter 3: Policy-Relevant Assessment of Health Effects Evidence)

General Comments:
Chapter 3 is very well written and adequately presents the evidence assessed in the Ozone CD. I found it to be clearly presented, technically sound, and appropriately balanced across the health effects areas.

I also found the tables very helpful in summarizing the ozone-induced health effects.

The staff's characterization of susceptible groups that may be more sensitive to ozone exposure also appears justified and clearly documented in this first draft.

Specific Comments:

3-23; line 8 The statement that *epithelial hyperplasia follows a somewhat similar pattern to ozone-induced inflammation is not true* and should be deleted or corrected. Epithelial hyperplasia peaks soon after the inflammatory response, but is usually maintained in both the nose and lung, with continuous exposure. Epithelial hyperplasia/metaplasia also does not quickly repair after the end of exposure. Interestingly, long-term studies in rodents suggest that inflammation is maintained in the nasal airways with chronic continuous exposure (Harkema et al. Am J Respir Cell Mol Biol. 1997 May;16(5):521-30).

It must be noted that chronic episodic exposures may not have this same pattern of zone-induced tissue response for inflammation, epithelial hyperplasia or fibrosis. It must be emphasized that the described progression of morphologic effects is based primarily on the results of long-term animal studies using continuous, rather than episodic, exposures. This is an area for future research.

3-21; line 19 In a study by Harkema et al. (Response of macaque bronchiolar epithelium to ambient concentrations of ozone; Am J Pathol. 1993 Sep;143:857-66) monkeys were exposed to 0.15 and 0.30 ppm for 90 days and had airway remodeling of the bronchiolar airways at both concentrations.

Dr. Philip K. Hopke

Comments by Philip Hopke on 2nd Draft Ozone CD

This version of the CD is a substantial improvement on what was a good first draft. There are really no major issues with chapter 2 other than minor ones noted below.

Page 2-6 First Paragraph: This paragraph is one in which they could start to make the connection between ozone and other photochemical oxidants in the particulate phase. For example, 1,3, 5-trimethyl benzene has been shown to form oligomers (Kalberer et al., 2004) that would be difficult to chemically separate and identify leading to the underestimation of the carbon. Tolocka et al. (2004) see the polymerization of α-pinene with ozone. Isoprene reacts to produce methyl tetrols (Claeys et al., 2004) that would have reactive oxygen species as intermediates. Their *Atmospheric Environment* paper is mention in the Annex on AX2-28, but not the *Science* paper. There really should be some discussion of this as part of the discussion of SOA formation. The key point is that oxidants and SOA are interlinked. Thus, control of oxidants will have an impact on PM. This paragraph would be a good place to start making this point. The more detailed discussion of these cited papers would go into the Annex at page AX2-58 and 59.

There also needs to be a discussion of Docherty et al. (2004) showing that reactions such as α-pinene with ozone produce significant ROS.

Page 2-20, line 14. Isoprene is not a terpenoid. The important biogenic VOCs are isoprene and terpenoids.

Page 3-67. This paragraph and related materials really belongs in Chapter 2. This is describing chemistry and not exposure and thus belongs in the chemistry chapter.

"Ozone chemical reactions in the indoor environment are analogous to those reactions occurring in the ambient air (See discussion on atmospheric chemistry in Chapter 2). Ozone reacts with unsaturated VOCs in the indoor environment, primarily terpenes or terpene-related compounds from cleaning products, air fresheners, and wood products. The reactions are dependent on the O_3 indoor concentration, the indoor temperature and, in most cases, the air exchange rate/ventilation rate. Some of the reaction products may more negatively impact human health and artifacts in the indoor environment than their precursors (Wolkoff et al., 1999; Wilkins et al., 2001; Weschler et al., 1992; Weschler and Shields, 1997; Rohr et al., 2002; Nrjgaard et al., 2005). Primary reaction products are Criegee biradicals, nitrate radicals, and peroxyacetyl radicals. Secondary reaction products are hydroxy, alkyl, alkylperoxy, hydroperoxy, and alkoxy radicals. Reactions with alkenes can produce aldehydes, ketones, and organic acids (Weschler and Shields, 2000; Weschler et al., 1992)."

The point to be made in Chapter 8 is that SOA and photochemical oxidants are interconnected. The availability of ozone leads to reactions with the isoprene and terpenoids leading to both gas and particle-phase oxidants. The limonene and other indoor air reactions really do not rise to the level of importance for the integrated summary chapter.

References

M. Claeys, B. Graham, G. Vas, Wu Wang, Reinhilde Vermeylen, Vlada Pashynska, Jan Cafmeyer, Pascal Guyon, Meinrat O. Andreae, Paulo Artaxo, Willy Maenhaut, Formation of Secondary Organic Aerosols Through Photooxidation of Isoprene, Science 303: 1173-1176

Docherty, K. S., Wu, W., Lim, Y. B., Ziemann, P. J., 2005: Contributions of organic peroxides to secondary aerosol formed from reactions of monoterpenes with O3. *Environ. Sci. Technol.*, 39, 4049-4059.

Gao, S., et al., (2004), Particle phase acidity and oligomer formation in secondary organic aerosol, *Environ. Sci. Technol.*, 38, 6582-6589.

Kalberer, M., et al. (2004), Identification of polymers as major components of atmospheric organic aerosols, *Science*, 303, 1659-1662.

Tolocka, M., P., M. Jang, J. M. Ginter, F. J. Cox, R. M. Kamens, and M. V. Johnston (2004), Formation of oligomers in secondary organic aerosol, *Environ. Sci. Technol.*, 38, 1428-1434.

Dr. Michael T. Kleinman

Michael T. Kleinman, Ph.D
December 16, 2005

Comments on CD Chapter 5

Overall this chapter is well written and provides an objective summary of the sometimes confusing studies presented in the Appendix. There are several points that are made in the CD that don't get carried over to the Integration and Staff paper level.

One important issue is that of attenuation (or tolerance) of some effects following repeated exposures. For example, points made on p 5-38, L 12-15 and p 5-39, L 25-29 should be carried through to the Integration and Chap. 3 of the Staff Paper.

Specific Comments:

P 5-3, L 16 (and others) nonanal is spelled differently in different sentences. The word should be spell checked.

P 5-7, L 21 Define diffusive resistance

P 5-24 L25 -30 The discussion of C x T relationships should be presented in a more complete and less qualitative manner. C x T assumptions are implicit in application of the NAAQS and the topic needs to be discussed with respect to environmentally relevant O3 levels.

P5-43, L 4-7 These findings should be integrated with those from the sections on acute and subacute exposures.

P5-45, L 18 insert the word …pulmonary function <u>decrements</u>…

P5-52, L9 I don't think that this shift in injury pattern should characterized as a form of protection since it represents a shift in the location of injury rather than an alleviation of injury.

Dr. Allan Legge

December 19, 2005

FINAL REVIEW COMMENTS: Allan H. Legge

Air Quality Criteria for Ozone and Related Photochemical Oxidants (Second External Review Draft), August 2005, EPA/600/R-05/004cB

General Comment: Chapter 3. Environmental Concentrations, Patterns, and Exposure Estimates.

Reference is made in the text to "Some associated metrics for vegetation exposures" (pg 3-6, lines 19-20) in the ANNEX AX3. A number of ozone metrics are found in the ANNEX AX3 such as the number of hours equal to or greater than 0.08 and 0.10 ppm (N100) , seasonal 7- hour, W126 and SUM06. Section AX3.2.1 , National Distribution of Metrics for Characterizing Exposures of Vegetation to Ozone (pages AX3-27 to AX3-39) provides a series of figures showing the distribution of several of these indices, N100, W126 and SUM06, in different sections of the US. This is informative. That being said, there needs to be a better linkage with Chapter 9 and the ANNEXAX9 both from the perspective of the authors of Chapter 3 and it's ANNEX and the authors of Chapter 9 and it's ANNEX. The purpose is not only for completeness but also for consistency and clarity for the reader.

Specific Comments: Chapter 3. Environmental Concentrations, Patterns, and Exposure Estimates.

1. Pg 3.2, line 3.
   Suggest this read "Several different types of air quality metrics have been suggested for evaluating exposure of vegetation to O^{3}"
2. Pg 3-8, Figure 3-4a-c.
   The 'a', 'b' and 'c' designations are missing from the figure but are indicated in the legend.
3. Pg 3-10, Figure 3-5a-d and pg AX3-17, Figure AX3-11a-d.
   At the top of Figure 3-5a and Figure AX3-11a under the Theodore Roosevelt National Park heading, the number of hours of observations are shown. Above the 1998 box and whisker plot a total of 1808 hours of observations is shown. This number of hours of observations is considerably less than for other years. The reason for this should be indicated at least in the figure legend. The data on page AX3-21 in Table AX3-3 (cont'd) seems to suggest that the air quality monitoring site must have been moved sometime during 1998 so that only a partial ozone monitoring season was measured.
4. Pg 3-32, Figure 3-15 Legend, line 2.
   Should read " - - - - . Values shown are averages from April to October 2000 to"

Specific Comments: Volume III/Preface/Abbreviations and Acronyms

1. Preface, page III-iii, para 1, bottom three lines.

It is noted that EPA in 1997 set an 8-h O_3 NAAQS that is currently in force with the 1-h O_3 standard. According to the Federal Register (1997) [see Vol 62, Number 138, Friday July 18, 1997, Rules and Regulations, page 38856] "The current 1-hour primary standard is replaced by an 8-hour standard at a level of 0.08 parts per million (ppm) with the form based upon the 3-year average of the annual fourth-highest daily maximum 8-hour average O_3 concentrations measured at each monitor within an area."

2. Preface, page III-iii, para 3, line four from bottom.

This should read "to provide inputs to associated Ozone Staff Paper analyses - ."

3. Abbreviations and Acronyms, page III-xxvi, KROFEX

Should read "Kranzberg Ozone Fumigation Experiment"

Overall Comments: Volume III Chapter 9 and ANNEX AX9 Environmental Effects: Ozone Effects on Vegetation and Ecosystems, Volume I, Executive Summary, E.9 Vegetation and Ecological Effects (pages E-28 to E-32).

(1) This 2nd draft revision of Chapter 9 into a summary overview (Chapter 9) and the detailed scientific information in ANNEX AX9 is a major improvement. The authors are to be commended. The ANNEX AX9 is a comprehensive compilation of the scientific information published since the 1996 Ozone Air Quality Criteria Document (AQCD). It is a balanced and thoughtful presentation of the available information. The interweaving of key information prior to the 1996 AQCD with the more recent scientific information is both useful and appropriate. That being said, more effort is required by the authors of the summary overview (Chapter 9) to ensure that there is consistency between the key information presented in Chapter 9 and the detailed information presented in the ANNEX AX9.

(2) As noted above under 'General Comment' for Chapter 3 and the ANNEX AX3, there needs to be a better linkage with Chapter 9 and ANNEX AX9 especially as it relates to the exposure metrics used. Reference to Figure 3-6, page 3-16 and Figure 3-7, page 3-16 would be helpful. This relates to the matter of the 'Vertical Variations in Ozone Concentrations' (see pages 3-15 to 3-17). One of the key issues with respect to using indices (i.e. metrics) is the ozone concentration at canopy height versus that measured at the height of the air intake at an air quality monitoring trailer. There is a decrease in ozone concentration with height. A clearer discussion of this in both Chapter 9 and the ANNEX would be very helpful.

(3) One of the problems in the text relates to the use of plant names. A summary listing of common plant names used along with their Latin names and describers needs to be added.

(4) The Executive Summary provides a useful point form summary of the key

information. It would be helpful for the reader for there to be appropriate cross references to the location of this key information in Chapter 9 and ANNEX AX9.

(5) There is repeated reference in the text to the matter of detoxification. This is fine but it needs to be put into the proper context. There is more involved than simply detoxification with ozone exposure. One can look at the reaction of plants to ozone exposure as the following series of responses: (1) stimulation; (2) detoxification and/or compensation and repair; (3) adverse effect expressed as some defined biological endpoint such as visible symptom development, decreased growth and/or decreased yield; and (4) carry-over effect (re perennials). The reaction of plants to ozone exposure is not simple.

(6) There needs to be a more concise discussion with respect to the way in which OTCs factors such as temperature, relative humidity, ozone profile, wind/turbulence profile and optimal nutritional status can modify plant response to ozone. This discussion should be related to the discussion of the uncertainty resulting from using ozone concentration response functions developed from OTC experiments.

Specific Comments: Volume III Chapter 9

1. Pg 9-1, lines 20-22.

It is indicated that "The FACE systems have substantiated earlier growth and yield results for crop and tree species obtained in open-top chamber (OTC) systems." There are no statements or references which clearly and directly provide support for this statement. The closest statement is found on page 9-3 (lines 29-31) and page 9-4 (lines 1-3) where it is noted that ozone symptom expression in quaking aspen was generally similar across the OTC, FACE and sites along a gradient supporting the previously observed level of variation among aspen clones in OTC studies. The same information is found on page 9-15 (lines 28-30) and page 9-16 (line 1) where it is stated that "These studies (i.e. Aspen FACE) showed that O_3 symptom expression was generally similar in OTC's, FACE, and also at sites along an ambient O_3 gradient, supporting the previously observed variation among aspen clones obtained using OTCs (Karnosky et al., 1999)." It is indicated on page 9-4, lines 3-5, that "While this perhaps represents the first time direct comparisons were made (sic across exposure methodologies), it supports the use of OTC data in the development of O_3 response functions for individual species." It is a significant jump in our understanding to assume that similarity in visible foliar symptoms on given plant species due to ozone exposure can be equated to the similar growth and yield responses on those same plant species when different exposure methodologies are used. This same assumption is made in ANNEX AX9. It is noted on page AX9-44, lines 8-10, for example, that "- - - production of visible injury - - have not been shown to lead directly to a loss of productivity due to possible compensation by the remaining tissue."

2. Pg 9-9, lines 24-26.

This is a matter of lack of consistency between the overview summary and the

ANNEX AX9. It is noted that "- - - ,it appears that any shift away from the nutritional optimum may lead to greater O_3 sensitivity; but the shift would have be substantial before a significant effect on O_3 response was observed." In the ANNEX AX9 on page AX9-137, line 26-29, there is a discussion of the ozone /nitrogen interaction. The effect of ozone is greatest when nitrogen availability is optimal but the effect of the ozone decreases with both increasing nitrogen deficiency and excess nitrogen.

3. Pg 9-12, lines 2-12.

This information suggests that the important role for higher ozone concentrations can be inferred from the reduction in higher ozone concentrations and the general forest improvement. The role of nitrogen in mediating the forest response to ozone in the San Bernardino Mountain area needs to be considered.

4. Pg 9-14, line 4 and line 7-9.

There is confusion here. Reference is made to AOT40 but AOT60 is defined. Also emphasis is primarily on SUM06 with little reference to AOT40 or W126. Chapter 3 discussed a number of different metrics. There needs to be better linkage between Chapter 3/ ANNEX AX3 and Chapter 9/ANNEX AX9. The case has not been made as to why SUM06 has been chosen as the metric. It is noted on page 9-11, lines 2-3 that "Since the 1996 O_3 AQCD, there has been no direct experimental testing of the adequacy of exposure indices proposed in 1996;".

Specific Comments: Volume III Annex AX9

1. Pg AX9-22, line 11.

Remove describer of epithets for consistency with the rest of the text.

2. Pg AX9-44

i) line 16.

Suggest this read "continue to be studied - - is an appropriate model plant for"

ii) line 19.

Rather than "inefficient choice" suggest "inappropriate choice".

3. Pg AX9-48, line 5.

Reword "(for both concentrations of external O_3). Suggest '(from both sources of external O_3 concentrations)'.

4.Pg AX9-48,para 1 and pg AX9-49 Figure AX9-5.

Reference is made to "0.88" as the higher level in the text but to "0.821" in the figure legend. When 'rounded', this would '0.82' not '0.88'. Which is correct?

5.Pg AX9-89, lines 13-16.

Reference is made to the work of Smeulders et al. (1995) with no mention of the fact that the work was on mature and juvenile Douglas Fir. This should be added. Also in line 14 "mg/m^3" should read "Fg/m^3 ".

6. Pg AX9-90, line 28.
Define “MDA” in text.

7. Pg AX9-92, line 20.
Remove describer from epithet for consistency in the text.

8. Pg AX9-107, lines 11-19 and pg AX9-174, lines 11-12.
This is an odd paragraph. The intent is unclear. The authors appear to be blaming the research community for not providing the authors with the information needed by the authors by saying that the published work reflected the “narrowly focused interests of individual researchers or groups”. This is not appropriate as phrased. On page AX9-174, lines 11-12, where it is noted that part of the problem is “due to the overall lack of funding for such research” is more balanced and objective.

9. Pg AX9-108, line 29.
Should read “- - - - - - of the roles of environmental”

10. Pg AX9-111, line 2.
Define “MnSOD” in text.

11. Pg AX9-115, line 5.
Delete “but”.

12. Pg AX9-119, lines 27-29.
Need to explain the meaning of “standard O_3 exposures”.

13. Pg AX9-124, lines 4-9.
Reference is made to classification of the four aspen clones as ‘advantaged’ or ‘disadvantaged’. How does this classification relate to their ozone sensitivity?

14. Pg AX9-129, lines 1-6.
It is suggested that decreased grain yields are caused by the shortened growing season due to the rapid (i.e. early) onset of senescence from increased assimilation rate and increased temperature. This could also be due to an increased respiration rate due to increased temperature which could more than offset the increased assimilation rate.

15. Pg AX9-171, line 28.
Should read “ - - - on the impacts of UV-B radiation per se.”

16. Pg AX9-197, line 30.
Should this read “averaged” or ‘average’?

17. Pg AX9-201, lines 30-31.
    Sentence unclear. What is “54.4"?
18. Pg AX9-204, line 21.
    Should read “effects-based emissions abatement strategies.”

19. Pg AX9-208, lines 1-14.
    The case is presented from a model simulation of Ponderosa pine growth over a 40 year period that “improvement in growth was assigned to improved air quality” in the San Bernardino National Forest. While improved ozone air quality may be an important factor, the significant role of increased N deposition must also be considered.

20. Pg AX9-214, line 3.
    Should read “visible injury in cutleaf coneflower (*Rudbeckia laciniata* var. *digitata*) populations in Great Smokey Mountains National Park was unlikely to be due to differences”. Note the ‘coneflower’ is not in the genus Echinacea.

21. Pg AX9-221, lines 21-25.
    Refer to ‘Specific Comment 19' above. The role of N deposition needs to be considered.

22. Pg AX9-234, lines 3-5.
    It is noted that “The advantage of the regression approach is that exposure-response models can be used to interpolate results between treatment levels.” This advantage is true ‘assuming’ that the response of the vegetation to ozone exposure is linear from elevated to low ozone concentration. This is unlikely.

23. Pg AX9-260, lines 2-16 and Table AX9-21.
    This is a discussion of Table AX9-21 which does not appear until page AX9-275. The actual table needs to be moved to appear closer to the text explaining the table.

24. Pg AX9-269, line 28.
    Should read “Spreading dogbane (*Apocynum androsaemifolium*) has been”

25. Pg AX9-270, lines 19-21.
    Reference is made to Heagle et al (1998) where it is noted that the authors concluded that “Although chamber effects on yield are common, there are no results showing that this will result in a changed yield response to O_3.” This is a very selective quote since later in the text on page 174 in para 2 in Section 7.5 Research Needs the following is noted. “Open-top chambers cause major changes in wind velocity, light profile, air velocity profiles, and O_3 concentration fluctuation compared to ambient. Chambers can affect plant growth and yield. Thus, there is a lingering question as to whether plant response to O_3 in opene-top chambers is similar to that in commercial fields.”

26. Page AX9-270, lines 5-31, Section AX9-5-4-5 Scaling Experimental Data to Field Conditions.
    The reader is left with the impression that the authors are 'desperate' to be able to justify the extrapolation of the results of OTC experiments to the ambient environment despite all of the underlying uncertainties associated with the OTC results. This does not mean to suggest that OTC results are not good science but rather that the extrapolation of the OTC results to 'quantitatively' reflect the response of the vegetation in the ambient environment is questionable.

27. Pg AX9-276, lines 9-10.
    Should read " - - and late-season planted Bahia grass (*Paspalum notatum* cultivar *Pensacola*) in OTCs to CF - - - ."

28. Pg AX9-278, lines 25-26.
    Should read " Germander speedwell [*Veronica chamaedrys*] grown - - ."

29. Pg AX9-287, lines 28-31 and pg AX9-288, lines 2-5.
    The logic presented here requires a leap of faith. The fact that O_3 - symptom expression was "generally similar in OTC's, FACE and ambient gradient sites" does not mean that all of the results from OTC experiments can now be used. Visible symptoms are but one endpoint and are unlikely to be diagnostic of other endpoints in a qualitative sense.

30. Pg AX9-322, line 22.
    Suggest this read " largely as a result - - - as well as emissions of nitrogen oxides."

31. Pg AX9-329, lines 11-14.
    Should read " 1999). Short-lived (50-80 years) species such as knobcone pine (*Pinus attenuata*) and Coulter pine (*Pinus coulteri*), which - - - -."

32. Pg AX9-331, line 3 and line 13.
    Should read "common plantain" and not "sunflower".

33. Pg AX9-336, line 7.
    Should read "value during the growing season."

34. Pg AX9-343 -Pg AX9-346, Section AX9.6.4.2 Species and Populations.
    There needs to be mention of the role of the breeding system of the plant. Plants that are self-pollinated have a narrower genetic base and plants that are cross-pollinated.

35. Pg AX9-359, lines 30-31.
    This sentence is unclear as written. What is "Reconstruction of chlorophyll"?

36. Pg AX9-366, line 30.

Should read "…1997). Taken together, these results suggest that there may not be an association between growth of"

37. Pg AX9-367, lines 3-18.

There are number of references to plants from Kohut et al. 2000. The text has a mixture of common plant names as well as Latin names. It is assumed that this reference has both common names as well as Latin names. For consistency in the text, the common names should be followed by the Latin names when first mentioned in the text. The following will need to be verified.

i) line 12.

big-leaf aster (*Aster macrophyllus*)

ii) line 13

small sundrops (*Oenothera* spp.)

iii) line 16

Canada bluejoint grass (*Calamagrostis canadense*), wild radish (*Raphanus raphanistrum*), and Canada mayflower (*Maianthemum canadense*)

38. Pg AX9-396, lines 26-28.

This point should be noted in the summary as it currently is the major weakness. As noted by Adams (1999),better and more representative physical and natural science data will do more to improve economic assessments than efforts to fine-tune the economic assessment techniques.

Dr. Morton Lippmann

REVIEW COMMENTS – OZONE CD, 2nd DRAFT – M. LIPPMANN

Chapter 2. Physics and Chemistry of Ozone in the Atmosphere

General Comment:
The revised Chapter 2 incorporates the Panel's constructive comments from the first draft and is much improved. While it is an excellent summary of most of the current knowledge that is relevant to the setting of an ozone NAAQS, it fails to provide an adequate discussion of the chemistry that accounts for the secular rise, over the past century, of the global background concentration of O3 from about 10 ppb to about 35 ppb, and its implications to NAAQS attainment.

Chapter 3. Environmental Concentrations, Patterns, and Exposure Estimates

General Comment:
The revised Chapter 3 incorporates the Panel's constructive comments from the first draft and is improved. I find it to be an excellent summary of current knowledge that is relevant to the setting of an ozone NAAQS.

Chapter 4. Dosimetry, Species Homology, Sensitivity, and Animal-to-Human Extrapolation

General Comment:
The revised Chapter 4 incorporates the Panel's constructive comments from the first draft and is much improved. I find it to be an excellent summary of current knowledge that is relevant to the setting of an ozone NAAQS.

Chapter 5. Toxicological Effects of Ozone and Related Photochemical Oxidants in Laboratory Animals and *in vitro* Test Systems

General Comment:
The revised Chapter 5 incorporates the Panel's constructive comments from the first draft and is much improved. I find it to be an excellent summary of current knowledge that is relevant to the setting of an ozone NAAQS.

Specific Comments:
p. 5-4, line 10: change "the' to "that".

p. 5-11. line 25: define "PE".

p. 5-17, lines 27, 28: Here, for the first time, concentrations are expressed in mg/m3. They should be translated to ppm for consistency.

p. 5-18, line 3: change “mg” to “mg/m3”, or define how the dose was delivered.

p. 5-24, lines 23, 24: This statement is misleading in that it implies that concentration is the dominant factor. It may be somewhat more important than duration and ventilation rate, but these latter factors do have substantial influences.

Chapter 6. Controlled Human Exposure Studies of Ozone and Related Photochemical Oxidants

General Comment:
The revised Chapter 6 incorporates the Panel’s constructive comments from the first draft and is much improved. I find it to be an excellent summary of current knowledge that is relevant to the setting of an ozone NAAQS.

Specific Comments:
p. 6-3, line 17: change “2h or less” to “1-2h”.

p. 6-4, line 19: insert “young” before “white”.

p. 6-22, line 10: change “instant” to “instance”.

p. 6-32, line 27: change “from” to “of”.

Chapter 7. Epidemiologic Studies of Human Health Effects Associated with Ambient Ozone Exposure

General Comment:
The revised Chapter 7 incorporates most of the Panel’s constructive comments from the first draft and is much improved. With the exception of its treatment of the epidemiology on chronic exposure to O3, I find it to be an excellent summary of current knowledge that is relevant to the setting of an ozone NAAQS.

Specific Comments:
p. 7-6, line 2: “non-ambient source exposures” needs to be clarified. Does it refer to the ambient air O3 that is present in reduced concentrations indoors, to emissions from copying machines, or both?

p. 7-75, line 7: change “lead” to “led”.

p.7-81, line 8: change “was” to “were”.

p. 7-101, line 16: change “states” to “communities”.

pp. 7-101 and 7-102: I do not believe that the summary presentation of the Children’s Health Study (CHS) results provides a good description of the effects of chronic ozone exposure on the development of respiratory function capacity of children. I also think that Fig. 7-23 is far from the best illustration of the CHS findings, with respect to ozone, of this complex, ambitious, costly, and informative landmark study. I suggest replacing it with Fig. 3 from Gauderman (2004a), which shows FEV1 <80% of predicted vs. pollutant concentrations after 8 years of observation in CHS cohort #1. The p-values for O3, NO2, Acid Vapor, PM10, PM2.5, and EC were 0.89, 0.005, 0.01, 0.02, 0.002, and 0.006, respectively. It is hard to assign a role for O3 in the strong association of a significant deficit in this very stable lung function measurement, especially when it was so strongly associated with the concentrations of the other measured pollutants. A question that arises is whether these results are consistent with the findings from the cross-sectional analysis of Peters et al (1999b) on the same cohort before they were prospectively followed, which found some associations between their initial FEV1 values and ambient O3 levels? They could be, if the effect of O3 on lung function at age 8 was due to exposures that occurred before the age of 8 years.

pp. 7-103 through 7-105: Most of the other studies of lung function cited in this section, i.e., Ihorst et al. (2004), Frischer et al. (1999), Gong et al. (1998b) provided equivocal results, at best. The studies of Kinney et al. (1998), and Tager et al (1998) on attained lung function in college freshman indicate some significant associations with estimated lifetime cumulative O3 exposure, but the influence of the co-exposures to other ambient air pollutants was not considered as thoroughly as in the CHS. Alternatively, the effects attributed to O3 could have been due to early lifetime exposures to O3.

p. 7-106, lines 1 –5: This closing paragraph for Section 7.5.4 needs to be reconsidered in view of my discussion above on pp. 7-101 through 7-105.

p. 7-105, line 29: “Tager (1993)” was merely summarizing the content of another paper in the same volume, i.e., Lippmann, M. Use of human lung tissue for studies of structural changes associated with chronic ozone exposure: Opportunities and critical issues. Environ. Health Perspect. 101(Suppl. 4):209-212 (1993).

7-109, line 25: delete “it is not clear to what extent”.

7-109, line 26: insert “not” before “based”.

7-110, line 14: change “was” to “were”.

7-110, line 25: This statement is misleading, at best. O3 may be highly correlated with other criteria pollutants at times but, of all the criteria pollutants, it is often the least well correlated with the others.

7-113, line 30: change “Few” to “Only a few”.

7-130, lines 17 &18, and 30. This issue of correlations between O3 and the other criteria pollutants is stated quite differently in these two places on the same page. As noted above, I prefer the interpretation presented on lines 17 and 18.

7-131, line 13: What kind of research will resolve this issue?

7-138, line 1: insert “into” after “penetrate”.

7-145, line 10: change “may lead” to “leads”.

7-145, line 14: insert “of asthmatic children” after “study”.

7-145, line 22: change “asthma subjects” to “subjects with asthma”.

7-145, line 28: insert “more” before “protection”.

7-145, line 29: add “than the general public” after “exposures”.

7-146, line 26: change “Few” to “A few”.

7-147, line 1: The issue is poorly stated. 10% of the mortality in a population of about 20 million is hardly a small number. Perhaps the limited statistical power for the young children is due more to fewer competing causes.

&-150, line 7: change “Less conclusive” to “Inconclusive”.

7-150, line 36: add “and asthma symptoms in children” at end of sentence.

7-151, line 40 - 42: The effect of age on lung function responses is hardly limited to “one epidemiologic study”. What about all of the quite consistent results of many clinical laboratory studies?

Chapter 8: Integrative Synthesis: Ozone Exposure and Health Effects

General Comment:
The revised Chapter 8 incorporates many of the Panel’s constructive comments from the first draft and is clearly an improvement. I find that it is reasonably close to being an adequate summary of current knowledge that is relevant to the setting of an ozone NAAQS. However, Section 8.7, Summary and Conclusions for Ozone Health Effects has a subsection (#3 on Health Effects of Long-term exposures to Ozone) that fails to address the epidemiologic literature. A summary bullet is clearly needed to help to justify the eventual Staff Paper decision to not recommend an annual average O3 NAAQS.

Specific Comments:

p. 8-1, line 7: change “tropospheric” to “boundary layer”.

p. 8-2, line 1: insert “also” before “exert”.

p. 8-9, line 4: insert “large population groups” before “O3”.

p. 8-9, line 5: change “O3 exposures of large population groups” to “ambient O3”.

p. 8-9, line 10: insert “and doses” before “than”.

p. 8-9, line 28: insert “much” before “lower”.

p. 8-22, lines 22 & 23: state the NO2 and SO2 concentrations.

p. 8-23, line 2: insert “co-pollutants,” after “gender,”.

p. 8-23, line 12: delete ”novel”.

p. 8-23, line 29: insert “peak expiratory flow rate (PEFR) after “(FEV1),”.

p. 8-24, line 8: insert “at resting ventilation” after “exposure”.

p. 8-29, line 16: insert the number of hours.

p. 8-30, line 30: change “New studies” to “Studies first”.

p. 8-31, lines 11-22: The studies referred to in this paragraph do not have reference citations, as do the others in this section.

p. 8-32, line 19: change “concentration” to “exposure”.

p. 8-32, line 22: change “concentration” to “exposure”.

p. 8-35, line 20: change “Few” to “A few”.

p. 8-41, line 26: change “children” to “healthy children and young adults,”.

p. 8-42, line 20: change “pulmonary function” to “FEV1”.

p. 8-42, line 27: insert “for FEV1” after “slopes”.

p. 8-65, lines 29 & 30: these %s must refer to a specific exposure condition (concentration, duration, and ventilation). What was it?

p. 8-65, line 2: insert “older” before “adults”.

p. 8-65, line 3: delete “older” and “(>60 yrs)”.

p. 8-67, line 1: change “children and asthmatics “to “asthmatic children”.

p. 8-82, line 21: add “Overall, the studies cited in the previous CD and the newer studies demonstrate that:”.

p. 8-84, line 4: change “do not suggest such” to “were less consistent in their support of”.

p. 8-86, line 17: insert “that is especially susceptible” before “for”.

Dr. Frederick J. Miller

Dr. Fred J. Miller
December 16, 2005

Dosimetry, Species Homology, Sensitivity, and Animal-to-Human Extrapolation
Chapter 4

General Comments

This version of Chapter 4 is greatly improved from the first draft.

- There are still some areas for which graphic illustration of the points being made would significantly improve the ability of the reader to follow the author's discussion.
- In Section 4.2, the authors should also make the point that the dosimetry models can translate human exposure scenarios as well as animal exposure data.
- In this chapter, the focus of dosimetry statements centers around uptake rather than presenting results using dose metrics that likely relate more to the biological effects that result from exposure to ozone. As such, statements like the one on page 4-4 (line 7) are somewhat misleading. Yes, increasing flow or breathing frequency decreases ozone uptake on a percentage of inhaled ozone basis, but the fact is that the ozone tissue dose is greatly increased in the real world scenario where increased breathing frequency is usually associated with exercise and this scenario results in significant increases in the mass of ozone delivered to lung tissue.
- The discussion of the Mudway and Kelly (2004) meta-analysis includes a statement that a large-scale study could determine a possible ozone threshold for inflammatory responses. This is a particularly important postulation that has significant implications for the level of the standard and warrants more discussion.
- In Section 4.3, normalization to dose must be done before making any comparisons among species as to which is the most sensitive for a particular biological response. (See, for example, page 4-15 (lines 8-13).

Specific Comments

p. 4-2, l. 15 Insert a comma after ELF.

p. 4-5 The last sentence in the legend to Figure 4-2 makes the point that the uptake fraction is better correlated with the volume of the conducting airways. The authors should point out either here or in the text that this result fits with the results of Overton et al. (1996) relative to the influence of tracheobronchial expansion on the delivered dose of ozone.

p. 4-5, l. 8 The phrase "who then inhaled to a 20 ml bolus …" is confusing and needs to be restated.

p. 4-6, l. 15 Check the units on rate of inspiration. I believe they should be L/sec.

p. 4-7, l. 1 Here is a place where a figure would be useful in describing the results of the ozone bolus experiment.

p. 4-8, l. 5 Insert a comma after resistance.

p. 4-8, l. 21 While there was a statistically significant reduction in uptake over the 15 minute period, I doubt that the change would impart a biologically significant difference. The authors might comment on this possibility.

p. 4-10, l. 16 Insert a comma after equations.

p. 4-11, l. 25 Strongly recommend a graph be added showing the meta-analysis results of the 23 human chamber studies.

p. 4-12, l. 9 Add an “s” to “rat”.

p. 4-13, l. 10 Clarify whether it is the inter-individual differences in fractional uptake that vary as stated or the fractional uptakes themselves. To get an inter-individual differences in fractional uptake of 0.97, one individual would have to have an uptake fraction of 0.03 and the other a fraction of 1.0, which is highly unlikely.

p. 4-15, l. 7 The discussion of protein levels in BALF should be reworded. An interspecies dosimetric adjustment was done for this endpoint by Miller and colleagues that integrated studies in the various species. In addition, the work by Plopper et al. (Am. J. Respir. Cell Mol. Biol. 19:387-399, 1998) reported tissue doses in monkeys of $^{18}O_3$ that showed a lower respiratory tract pattern very similar to what Miller and colleagues predicted 20 years earlier for humans (Similarity between man and laboratory animals in regional pulmonary deposition of ozone. Miller FJ, DB Menzel, and DL Coffin. Environ Res 17:84–101, 1978).

P. 4-16, l. 18 The statement that cytokine responses in guinea pigs and humans are both qualitatively and quantitatively similar is suspect relative to “quantitative”. The experiments upon which this statement is based involved in vitro exposures. Extension to the in vivo situation is not direct as can be seen from the results of the studies by Hatch et al. (1994), which are discussed on page 4-19.

Toxicological Effects of Ozone and Related Photochemical Oxidants in Laboratory Animals and In Vitro Test Systems
Chapter 5

General Comments

This version of Chapter 5 adequately describes current knowledge about the animal toxicological results of ozone and other photochemical oxidants. While the summaries at the end of each major section could be more succinct, they do capture the major findings.

Specific Comments

p. 5-2, l. 20 The statement that ozone diffuses no more than 0.1 µm to 0.2 µm into the ELF is made followed by a statement that cell damage most likely results from the reaction of ozone with PUFAs to form stable but less reactive products. This review strongly disagrees with this concept for the alveolar region since the ELF there is surfactant and the distribution of this material is extremely heterogeneous and is only about 0.02 µm thick in over 98% of the alveolar surface (see page 280 of Miller et al., 1995). Moreover, Chapter 5 is inconsistent in this regard because on page 5-8, line 1 the authors acknowledge that ozone can react directly with cell membranes in the distal regions of the lung where ELF is very thin or absent. The chapter needs to be made consistent internally on this subject.

p. 5-3, l. 5 The use of "deposition" here is incorrect since "absorption" is used relative to the removal of gases from the airway lumen.

p. 5-4, l. 12 Inset a comma after injury.

p. 5-7, l. 15 Delete the word "of".

p. 5-7, l. 18 UA does not appear in the list of abbreviations. An editor needs to search the document to ensure the list is complete.

p. 5-8, l. 14 Add an "s" to "rat".

p. 5-8, l. 27 Is the work by Ballinger et al. (2005) beyond the cutoff date for inclusion of publications? EPA needs to be consistent on their application of cut-off dates.

p. 5-15, l. 6 How do you express asbestos exposures in ppm unless it is the "shot" part of the aerosol and not the fiber portion? Please clarify.

p. 5-23, l. 22 Wording should be "in tracheal and bronchoalveolar zones".

p. 5-26, l. 13 The study by Savov et al. (2004) was conducted at such an unrealistically high level as to have no utility for ozone toxicology. This level of exposure causes rampant edema and obliterates the lungs of mice. This study should be deleted from the chapter.

p. 5-35, l. 11 The observation that continuous exposures may underestimate morphological effects is an important one that should be carried forward to the synthesis chapter since many of the animal studies involved continuous exposures.

P. 5-37, l. 1 The rating of susceptibility by Dormans et al. (1999) was done in the absence of first adjusting for the delivered dose of ozone, and thus, is not necessarily a valid conclusion.

p. 5-43, l. 22 Insert a comma after (1996).

p. 5-44, l. 18 Insert the word "the" before the word "trachea".

P. 5-53, l. 22 "protects" should be "protection".

Epidemiologic Studies of Human Health Effects Associated with Ambient Ozone Exposure – Chapter 7

General Comments

- Overall, the authors of Chapter 7 have done a good job of presenting the epidemiological evidence for various types of effects that can be associated with exposure to ozone. They have generally provided a balanced review of specific topics. Two areas of concern to this reviewer are the summarization of the case for chronic exposure causing mortality and the discussion on the effects of ozone on birth-related health outcomes (see Specific Comments below). In addition, the chapter summary makes note primarily of asthmatics as a potentially susceptible group but makes no mention of outdoor workers, a group for which the effects data seems to be quite solid. The writing could be more succinct in many places, but there are probably limited incentives for doing such at this point.

Specific Comments

p. 7-27	How do the authors explain a lack of a difference cross-day (Table 7-1c) in the Brauer et al study compared to the largest effect reported in Table 7-1b?
P. 7-61, l. 1	The discussion of the Tolbert et al. (2000) study on pediatric asthma emergency department visits is very revealing in that they showed that including PM10 and O_3 in the model caused the effects of these pollutants to become non-significant. So how much double jeopardy do we have here by using the study to support a PM10 effect and also an O_3 effect? This broadens to the whole issue of whether we are seeing effects of pollution as opposed to effects of O_3.
p. 7-67, l. 8	Replace "have" with "has".
Fig, 7-11	There is no discussion of this figure in the text.
p. 7-81, l. 8	"data were" not "data was"
p. 7-81, l. 22	Where do the authors get the 5% excess risk in mortality number?

p. 7-84, l. 13	The caveat raised here by the authors is a good one – namely that the 3 meta-analyses contained a large number of the same studies and so one would expect agreement in the combined risk estimates. But then this is ignored on line 21 when the authors state "These three studies, along with the earlier meta-analyses, provide strong evidence that O_3 is associated with mortality". Consistency is needed.
p. 7-87, l. 25	"There were" not "There was".
p. 7-108	Since asthma incidence is on the rise world-wide, how can the studies cited here be supportive of O_3 being causal in this development?
p. 7-114, l. 1	The conclusion/summary statement here is an overstatement of the need for concern about plausibility for the effects of chronic ozone exposure on lung cancer incidence and mortality. Surely the negative NTP chronic study for carcinogenesis using 1 ppm ozone should put this topic to rest.
p. 7-114	Section 7.5.9 on the effects of ozone on birth-related health outcomes could be significantly shortened. When are these negative or weak associations in epi studies going to be left just there and not touted as a cause for concern?
p. 7-117, l. 10	This reviewer does not agree that additional scarce research dollars should be devoted to examining the potential role of ozone on birth defects.
p. 7-117, l. 21	Strike "at present"
p. 7-117, l. 33	I recommend deleting the sentence calling for further examining the potential role of O_3 on birth defects.
p. 7-118, l. 12	Strike "further".
p. 7-118, l. 22	Replace "of much importance" with "important".
p. 7-129, l. 7	This reviewer fails to see why the authors contend that the larger effects of ozone for the warm season lend themselves to causal inference.
p. 7-138, l. 15	"levels" should be "level".
p. 7-148, l. 12	"alveolar" should be "alveoli".
p. 7-150, l. 4	The lack of sufficient studies to assess the long-term morbidity effects of ozone continues to be disturbing in view of the solid animal toxicological studies demonstrating chronic morbidity in rodents and non-human primates. This topic should be identified as a high priority research need.

Integrative Synthesis: Ozone Exposure and Health Effects
Chapter 8

General Comments

Overall, Chapter 8 represents a good job of presenting an integrated summary of the collective evidence for ozone health effects based upon dosimetry, animal toxicological, human clinical, and epidemiological data. A number of specific comments below reflect the need to clarify some points, to reword some sentences, and to correct or modify some interpretations of the published literature. However, these specific comments should not impart major problems for the authors. Worthy of note are the following:

- Table 8-1, Figure 8-9, and Figure 8-10 provide an excellent synthesis of various endpoints and the timeline over which these endpoints are probably affected by ozone exposure.
- The Hatch experiment involving animal and human cells and the difference needed in exposure concentration is a reflection of dosimetry factors more than it is a reflection of exercise per se.
- The section on dosimetry does not discuss one of the most important finding since the last CD, namely that anatomical dead space is a major driver of the delivered dose of ozone and probably accounts for a major part of the heterogeneity seen in responses in human clinical studies.
- The chapter fails to bring out that outdoor workers are likely to be a sensitive subpopulation. These individuals are likely to have repeated exposures over long time periods and have no choice but to be outdoors by the nature of their work.
- As in some of the other chapters, there is an inconsistency among the sections in the use of references to support the statements made.

Specific Comments

p. 8-7	The section of Policy Relevant Background concentrations, while interesting, goes nowhere because there is no bottom line provided as to what the monitoring and modeling data would support as a range for background ozone levels.
P. 8-9, l. 13	This sentence about the lack of exposure measurement studies has so many qualifiers that it is useless. The list of qualifiers includes “highly confident, broad, quantitative generalization” and belies the fact that the controlled clinical studies allow a reasonably accurate delineation between types of effects and their magnitude that occur in the general population compared to potentially sensitive subpopulations.
p. 8-9, l. 22	The material here and at the beginning of the next paragraph is redundant.
p. 8-19, l. 31	Strike “inhalability” from this sentence because inhalability is an issue for particles and not for gases.
p. 8-20, l. 7	What is meant by “physiological parameters”? The fact that there may be molecular differences between animals and humans for some elements is not as important if the functionality of the endpoint is the same between the species. Indeed, the physiological responses seen in

	pulmonary function changes in humans can be replicated in animals. Moreover, after adjusting for factors influencing dosimetry, biological responses have been shown to be similar between animals and humans (e.g., alveolar permeability)
p. 8-20	The section integrating dosimetric considerations fails to discuss one of the most important findings since the last ozone CD, namely the importance of the anatomical dead space for delivered dose of ozone. This has been shown both experimentally (Ultman and colleagues) and theoretically (Overton and colleagues).
p. 8-21, l. 30	The authors are missing the point about the Hatch study. It is not exercise per se that ended up being adjusted for at the higher exposure level, but rather that difference between rats and humans in both upper respiratory tract (URT) and lower respiratory tract (LRT) uptake of ozone. Overall uptake differs by a factor of 2 between rats and humans and URT uptake is greater in humans than it is in rats. These dosimetry differences lead to the difference needed in exposure levels in order to produce about an equivalent response in a LRT endpoint.
p. 8-25, l. 7-8	Insert a comma after “which” and after “subjects”.
p. 8-26, l. 5	Suggest modifying the sentence to read “… no new data…” to better reflect what the authors mean to convey.
p. 8-31, l. 28	Add an s to “rat”.
p.8-32, l. 20	Strike “also”.
Figure 8-4	This reviewer does not find this figure very useful. For each of the endpoints depicted in the figure, more than half of the studies in the meta analysis fall outside the 95% confidence intervals for the linear regression. A major reason for the poor fit is that Mudway and Kelly tried to depict in 2-D what really is better represented in 3-D. A 3-D plot using dose (represented as the product of concentration and minute ventilation), length of exposure, and the response (BAL PMN percentage) would yield a surface that would show the relative importance of dose and time and would show the complex nature of the response surface. Even better would be to get the individual data from the various studies (or even just use the group mean product of concentration and minute volume) and apply one of the available dosimetry models to obtain the predicted dose for each person per unit time and then make the 3-D plot.
p. 8-36, l. 9	Ozone has been more than implicated; it caused an increase in mortality with bacterial challenge. This sentence should be reworded.
p. 8-36, l. 28	The last sentence of this paragraph gives rise to a research need that could easily be addressed, namely ozone exposure of animals infected with RSV. RSV infections are important for infants and pre-school children.
p. 8-50, l. 24	As noted for Chapter 7, this reviewer sees no value in using limited research dollars to pursue potential effects of ozone on birth defects.
p. 8-53, l. 24	Shouldn’t the references used in this chapter have been discussed in one of the earlier chapters? The Schwartz (2004) reference was not

	discussed in Chapter 7.
Figure 8-10	In the legend to this figure “is” should be ‘are”.
p. 8-63, l. 6	Suggest rewording the sentence “however, extrapolation models … do exist”. Yes, all models will never be completely validated so naturally uncertainties will exist, but this sentence misses the point that the extrapolation and dosimetry models are indeed useful in assessing the potential for ozone to cause health effects in humans.
p. 8-64	The authors state that the sources of the heterogeneity are uncertain. However, information contained in earlier chapters of the CD point to a likely combination of anatomical dead space volume and individual susceptibility imparted by genetics as the primary sources of uncertainty. The authors should consider adding these points to the discussion in this paragraph.
p. 8-65	The statement about inflammation resolving completely should be restricted to low exposure levels.
p. 8-65, l. 19	This is not a sentence. Changing “resulting” to “results” would work.
p. 8-65, l. 30	Change “These are” to “There is”.
p. 8-66, l. 29	Strike the s from “supports”.
p. 8-67, l. 18	Insert a comma after “changes”.
p. 8-67	What are accumulation eosinophils? Clarify or most likely reword.
p. 8-68, l. 4	This sentence needs rewording.
p. 8-68, l. 21	Use “older’ rather than “old”.
p. 8-81, l. 16	Is the Georgia Medicaid claim file the best one can do for some of the statistics quoted here? This source represents a truncation of the population. Perhaps the authors could speculate on a broader data base.
p. 8-83, l. 25	Delete “on”.
p. 8-85, l. 25	To this reviewer, the speculation that ozone exposure may have the potential to induce URT alterations of a long-lasting nature is not warranted based upon the data available. There is a large gap between 0.5 ppm where effects were seen in animals and 0.12 ppm ozone where they were not.
p. 8-86, l. 7	There is a glaring omission in this section of reference to outdoor workers as a likely susceptible subpopulation. These workers have no choice but to be outside, often doing activities that require increased physical exertion that results in significantly increased doses of ozone being delivered to sensitive lung tissue. Moreover, these individuals are likely to have repeated exposures over long time periods.

Dr. Maria Morandi

Final Comments on Chapter 5: Toxicological Effects of Ozone and Related Photochemical Oxidants in Laboratory Animals and in vitro Test Systems.
Criteria Document for Ozone - 2nd Draft

Chapter 5 has been significantly improved and the Agency should be commended for their responsiveness to the Panel's recommendations in the review of the CD 1st draft . The revised version presents a more integrated assessment of the in-vivo animal data and the in-vitro studies. The enhanced cross-referencing between findings in these studies with those presented in Chapter 6 are very useful. In addition, it might be useful to add a separate section summarizing the linkages and consistent findings presented in the human and non-human biological effects and epidemiology chapters as a separate section in one of the chapters). Finally, the Chapter appropriately describes interspecies variability in response; it would also be useful to add some comment about inter-strain variability whenever the data are available.

There are some minor editorial changes:

1) In a couple of places in the Chapter, the phrase "study paradigm" is used when "study protocol" or "experimental protocol" or "exposure protocol" would be more appropriate.

2) Revise the text to indicate abbreviations the first time an acronym is introduced, and use the abbreviation thereafter. The whole document needs to be revised to make sure that all abbreviations or acronyms are described in the glossary

Page 5-1

Line 30 "….CD with new data, and basic conclusions are…"

Page 5-2

Line 26 '…in Figure 5-1. Studies published since…"

Page 5-3

Line 2 "…generated in BAL and also the rate…"

Line 14 "…protocol, the results are not useful for quantitative dosimetry,…"

Line 16: "nonanol" should be "nonanal"

Page 5-4

1 "…The results suggest that…"

Page 5-8

Line 27. There is a citation to a publication in 2005. This issue was discussed during the meeting the panel consensus was that the CD should indicate clearly the reasons for including a citation published after the deadline established for inclusion of findings in the current CD.

Page 5-12

Line 11: "...platelet derived growth factor, an inhibitor of apoptosis..."

Page 5-23

Line 31: "...while at higher exposures..."

Note: cut-off for referenced work??? Should be stated up front.

Mr. Rich Poirot

Comments on 2nd External Review Draft Ozone CD (August 2005), Chapter 10. Tropospheric Ozone Effects on UV-B Flux and its Role in Climate Change.
R. Poirot, VT DEC

Summary
Ozone can adsorb and scatter short-wave UV radiation and also adsorb longer wave IR radiation. Consequently, changes in tropospheric ozone concentrations over the US – such as those that have resulted, or will result from efforts to attain air quality standards – can potentially influence global and regional radiation budgets. Reduction in ambient air surface ozone concentrations might be anticipated to result in potential increases in UV-B flux and reductions in climate forcing effects. In both cases, any effects on radiation budgets can be anticipated to be very small with large uncertainties, and quantitative estimates of associated effects on human health or environment are not currently feasible.

For UV radiation effects, uncertainties are especially large. Its not currently clear if the relatively small reductions in peak ground-level ozone concentrations that might result from (or have resulted from) efforts to attain US ambient ozone standards will (or have had) any perceptible effects on UV-B radiation flux. A small increase in UV-B flux would likely result in health effects which are both negative (increased incidence of cataracts and skin cancers) and positive (increased vitamin D production with associated reductions in the incidence of several other forms of cancer) - such that it is not currently feasible to estimate (with any confidence) the direction of the effects (if there are any). While tropospheric ozone is a significant greenhouse gas, quantitative estimates of the reduced climate forcing benefits of (slight) reductions in surface ozone levels in (some parts of) the US would be small, highly uncertain, and of minimal value in determining appropriate levels for ambient air quality standards. EPA-led research efforts currently underway may place the Agency in a better position to consider such effects, as well as potentially more important effects on tropospheric ozone from climate changes in the next CD review cycle.

General Comments
I generally agree with staff conclusions that current uncertainties are sufficiently large to preclude any useful quantitative estimates of effects (which are likely to be very small in any event). I also don't think that EPA staff should be asked to spend a lot of additional resources revising this chapter. The climate change sections (10.3) are very clear, and have improved since the last draft. However, I really think the introductory sections (10.2.1, pp. 10.1 to 10-13) on factors governing UV-B flux at the earth's surface need more work. The writing is tentative, not well-organized and often unclear, while the focus seems too much on what is not known, rather that what is known. By contrast, the subsequent sections on factors affecting human exposure are stated more clearly, and the sections on climate change are extremely well-written.

Specific Comments

p. 10-1, line 18: What is “the global community”? The global UV-B research community?

p. 10-1, line 20: delete “over a period of several years”.

p. 10-1, line 21: “the importance…” (line 18) did not lead to the Montreal Protocol; the recognition did.

p. 10-2, line 9: What is the intended meaning of “though limited”? By whom? Compared to what?

p. 10-5, lines 10-12: I’m not sure that “daily and seasonal” factors are more important than latitude (at extreme latitudes there is No UV flux during winter) or why this would be useful information, if true. You might also change “higher” in line 12 to “larger”, as “higher” may imply more directly overhead – which would be a smaller zenith angle.

p. 10-5, line 22: I think you mean total column ozone, not “density”.

p. 10-5, line 26: This should be a continuation of preceding paragraph, not a new one. What is the meaning of “with very high efficiency”?

p. 10-6, lines 9-16: Can you add a brief explanation here of why the depletion has been about twice as great in the Southern hemisphere?

p. 10-7, lines 4-6: Is this really correct – that “UV radiation can traverse the stratosphere” (which contains 90% of the total column ozone) “with substantially lower probability of encountering a gas molecule” (of ozone).

p. 10-8, lines 1-10: This discussion of “single scattering” and “multiple scattering” regions, ozone (at different heights), clouds and aerosols – does not really shed much light on the central question: how important is UV absorption by tropospheric ozone compared to these other (much more important) factors? Also maybe provide some indication that most scattering by gases & non-cloud particles is ultimately in a forward direction – and not reflected back into space.

p. 10-8, lines 9,10: There is often substantial “direct” radiation passing through the troposphere (its not all diffuse). Also what’s the meaning of “or actinic”? Do you mean diffuse and actinic are the same thing, or that radiation is either diffuse or actinic? Neither is correct.

p. 10-9, line 6,7: “shallowest atmospheric depth” is an awkward way of saying this.

p. 10-9, line 10: What do you mean by “in principle”? and then “clouds have the largest influence on surface UV irradiance” - compared to what? Do you mean something like “On average, clouds have a larger influence on surface UV irradiance than atmospheric gases or pollution aerosols, but their effects are difficult to quantify for specific locations

and time periods." Can't you provide any quantitative indications of this "largest" cloud influence?

p. 10-9, lines 10-19: You make this sound impossibly complex, but I think algorithms for quantify cloud effects (and for estimating aerosol scattering & absorption) have been developed for and are routinely applied to site-specific UV radiation measurement data. The complex model you describe is only "required" to develop estimates over larger spatial scales.

p. 10-9, line 22: Need to define what is meant by "zonally averaged".

p. 10-9, line 26: This is the first time you use the term "erythemal". It needs to be defined, and I wonder why we are suddenly talking about skin response here?

p. 10-9, line 24-28: "model to measurement comparisons" needs some explanation. How did these lead to estimates of the specific UV reductions due to PM? If we have specific PM-related reductions of 20% (Greece) and 5-10% (Toronto), how do we know that these are "second only to cloud cover" if we don't know what the cloud effect is?

p. 10-9, lines 28-30: (I commented on this last time, but you've only half fixed the problem). The Barnard et al. (2003) paper had nothing to do with long-term (20-30 year) increases in combustion-associated black carbon and other PM. You are taking that quote (from the little JAWMA "implications" box) out of context. It is also incorrect: black carbon and other PM concentrations over North America have not increased (they have declined) over the past 20-30 years since the late 1970s – when emissions of primary PM and secondary PM precursors were at their maxima. This can be observed in both emission inventory and ambient PM measurement data.

What the Barnard paper did assess were the relative influences of black carbon, other PM, stratospheric ozone and surface ozone on surface UV-B measurements in Riverside/Rubidoux, CA (one of our most heavily polluted urban areas for both ozone and PM) during a 4-5 month period in 1997. The resultant regression equation was then tested (with remarkable success), at a remote eastern forest site in NC. Their analysis identified highly significant (inverse) associations between measured UV-B and PM-10, BC, and total column (primarily stratospheric) ozone, but despite repeated attempts to include local surface ozone as an explanatory variable, "it statistically did not meet the 0.05 significance level in this model." This (no significant influence) is an important finding that gets right to the point of this chapter. I suggest re-wording p-10, lines 26-30 to something like: "Model-to-measurement comparisons have estimated PM-associated reductions in ground-level UV flux in Greece and Toronto, Canada of 20% and 5-10% respectively (McKenzie et al. 2003). Barnard et al. (2003) employed a regression approach to explain variations in measured surface UV radiation at Riverside/Rubidoux, CA in relation to nearby measurements of ground-level ozone, black carbon, other particulate matter and (satellite derived) stratospheric ozone. They found highly significant effects from black carbon, other particulate matter and stratospheric ozone, but no significant effect from ground-level ozone (in an area with

some of the highest US surface ozone concentrations). The authors also suggested that the strong influences of black carbon and other PM may be masking our ability to detect trends in surface UV radiation from reductions in stratospheric ozone over the past several decades (Barnard et al., 2003).

p. 10-10, lines 2,3: "In the upper troposphere…gases … are vented from the surface" I assume you mean "gases present in the upper troposphere have been vented from the surface" (fix the English)! Also, this isn't entirely true as ozone in the upper troposphere may have been formed by secondary photochemical reactions of precursors emitted (by tall stacks) and formed well above the surface, or it may be due to intrusions from the stratosphere. Neither of these would be "vented or diffusing from" the surface."
p. 10-10, line 9: Change "within" to "over".

p. 10-10, lines 19,20: What did Koloutsou-Vakakis (2001) find in their analysis? We don't care what you read; we want to know what you learned.

p. 10-12, lines 1-4: Translate this into English. Do you mean something like: It's important to note that measurements of ground-level ozone reflect concentrations in a relatively thin layer at the earth's surface, while surface measurements of UV radiation reflect the influence of total column ozone (90 percent of which is in the stratosphere) as well as the even larger influences of tropospheric aerosols and clouds.

p. 10-31, line 23: "susceptibility" should be "susceptible".

p. 10-32, line 25: "is" should be "are".

p. 10-32, line 28: "spectrums" should be spectra".

p. 10-33, line 19 and p 10-34, lines 7, 8: Are there other terms that could be used to describe the concept of "insufficient" or "inadequate" UV-B radiation causing "premature deaths" primarily due to natural, latitude- related reductions in the northern US?

p. 10-34, lines 24-26: This list of factors with declining importance ends with "gas phase pollution" but does not include naturally occurring gaseous (stratospheric ozone) compounds (which are an order of magnitude more important than tropospheric ozone "pollution", some of which, itself, is natural.

p. 10-43, line 26: should be "increases in dark…" or increasing dark…"

p. 10-46, lines 1,2: Suggest moving "its vertical position (altitude) in the atmosphere" to before "and the albedo of the underlying surface".

p. 10-48, lines 1-6: A possible explanation for this trend of slight increases in low end O3 concentrations is that in polluted urban/suburban environments, ozone minima are artificially suppressed by NO titration during (night, winter, cloudy) times of reduced

photochemical activity. NOx emission reductions should logically be expected to both reduce peaks and increase troughs.

p. 10-48, line 25: Add “suggest” after “results”.

p. 10-49, lines 8, 9: The ozonesonde results displayed in Figure 10-7 are not “for surface concentrations only”, but rather from “between 630 and 400 hPa” – or roughly 4 to 7 km above the surface.

p. 10-51, line 2: “global” what? Globe?

p. 10-56, lines15,16: “The rate of increase in surface ozone …since 1980 appears to be slowing”. This is at best misleading. I think ozone over most of the US has been decreasing since 1990, and would probably show a net decrease since 1980 as well.

p. 10-57, line 10: I suspect the Jacob et al. (1993) paper observed these correlations were due to the effect of “temperature”, not “O3” on biogenic emissions, stagnation, etc.

p. 10-60, line 39: “roadband” should probably be “broadband”.

Dr. Armistead (Ted) Russell

Review of the Second Draft of the Ozone Criteria Document.

Armistead (Ted) Russell

In general, I am pleased with the modifications to the CD, as I do believe they have responded to my original comments. Their lack of treatment of "other oxidants" highlights the lack of information of those pollutants, particularly those in the condensed phase as part of particulate matter. The need to understand this possibly important type of pollutant should be highlighted.

E-6-2 "… , but THE few…"

E-8-8 Remove "inside and"

E-8-20 . Add "Reasons for this reversal in correlation are understood."

E-9-5 "…generation of CONDENSABLE ORGANIC MATTER AND ultrafine…"

2-16- 12: The Carter et al. ref. should just be Carter.

2-5-25 ". What is known of the chemistry of secondary …"

2-6-1: This paragraph somewhat repeats 2-5-21… I would remove the discussion from 2-5-21, but this is not a big deal.

2-18-2: I would just call it MM5, not the MM5.

2-19-27 "… two largest ANTHROPOGENIC sources…"

Chapter 3:

Policy-relevant background (PRB): The model results suggest that GEOS-CHEM does not reproduce the lowest values of ozone. It might be of interest to calculate the PRB at the various CASTNET sites by, first, developing an association between the modeled ozone and modeled PRB (hour-by-hour), and if that fit is reasonable, use that to calculate the PRB distribution from the observed ozone distributions. This might provide a more observationally-based PRB, blending model results and observations, and remove the observed "cut-off" in the PRB distribution now found from the modeling results. Next, they should assess the correlation (likely anti-correlation) between hourly ozone levels and the associated PRB on a grid-by-grid basis. This correlation structure could then be used in the exposure/risk assessment. Also, how does the model simulate surface (e.g., <2m) ozone under stable conditions? Might this be part of the reason the model does not capture the very low levels observed at CASTNE sites? This has implications for how one might simulate PRB.

Dr. Elizabeth A. (Lianne) Sheppard

Lianne Sheppard
Chapter 7 comments
December 2005

Overall
Organization and presentation: The organization and content of this chapter have been greatly improved, as has the presentation in the annex. I appreciate the shift in focus to more emphasis on point estimates and confidence intervals over statistical significance. The overview of the methods is improved but still needs refinement.

Section 7.1.3.1. on exposure assessment and measurement error: I appreciate the difficulty of briefly and appropriately covering this complex topic. The attempt is good but the section doesn't convey real clarity. I suggest revising to give the simple model for personal exposure as presented by Sheppard and then relating each of the other papers (specifically Zeger et al and Navidi et al) to this framework. This may allow the AQCD to convey greater clarity than is possible from reading the current literature. Study design for Navidi et al should be mentioned also since it is not a time series design.

7.1.3.3. on lags: It is quite likely that air pollution effects are distributed across multiple lags. The challenge is how to summarize these distributed lag effects. A single lag model still represents a distributed lag effect because the exposure series is autocorrelated. So there is a "ripple effect" in the estimate from a single lag model that captures a portion of the effects from other lags (see Schildcrout and Heagerty, 2005). The advantage of a single lag model is that it represents a realistic and simple to describe effect of what happens when air pollution changes one unit on a single day (and thus also carries with it some limited information on other days as well due to the autocorrelation in the exposure series). A distributed lag model gives an estimate for air pollution changing exactly one unit on all the distributed lag days. This is not a realistic contrast because that is not how the exposure series operates in time. The discussion about single and multiple day lag models needs to recognize these are different models that summarize the (unknown) underlying process differently.

Annex: The annex has been improved to show more detail about each study and to also provide a limited evaluative assessment. This evaluation is not always present and ideally would be included for every study. In particular, limitations of studies that restrict their interpretation or generalizability should be mentioned whenever possible. I also suggest an index to studies at the beginning so it is easier to find each study.

Evaluation of studies and papers: 7.1.4. (p 7-20 l. 17) discusses giving relatively more weight to studies with small standard errors among "well-conducted studies with adequate control for confounding". There is no mention of the judgment needed to determine which are indeed "well-conducted".

Cross-cultural comparisons of administrative outcomes: Comparing outcomes such as ER visits across nations can be difficult due to the differences in national health systems that will affect how these outcomes actually occur. Consider giving different weight to the European studies on p. 7-59, Figure 7-8.

General comments about modeling and epidemiology studies: (I include these to reflect a healthy skepticism. I am not recommending that these comments necessarily be incorporated into the AQCD. I think the perspective taken in the AQCD is one of several possible reasonable perspectives.)

Parameter testing vs. magnitude: A test for the statistical significance of a parameter can be valid even if the estimate is biased because a scale change in an estimate will be carried through to its variance and cancel in the test statistic. Since the epidemiology studies are based on concentration rather than exposure, testing is more likely to be valid than estimation (due to the attenuation bias of the RR parameter estimate). Unbiased estimation is more challenging than testing since the degree of attenuation of exposure almost certainly varies by season, geographic area, and susceptible population.

Model specification to capture full exposure history: The epidemiologic study models often don't (fully) incorporate biologically relevant exposure history. Typically a (generalized) linear model with only limited lags is specified to simply describe a relationship that is clearly quite complex. By not including the entire exposure history or accounting explicitly for development of tolerance, the epidemiologic models don't necessarily reflect the underlying biological process. On the flip side, by not including this exposure history, the epi models simply describe the relationship between exposure and response. In other words, they can answer the question of if exposure on the previous day increases, what happens to the health effect on average.

Meaningfulness of time series studies: Particularly relative to PM, I don't think it is currently understood how useful the time series study design is for estimating ozone effects. My concerns are predominantly based on our limited understanding about how personal exposure to ozone will be incorporated (from an underlying individual-level model) into the fitted time-series model conditional on ambient ozone concentration. Key issues are the reactivity of ozone and the strong seasonal variation of behaviors and ventilation practices that will affect population average exposure over time. Furthermore, because of its reactivity, it is unclear to what degree temperature or other pollutants should be adjusted for as confounders in time series studies of ozone effects.

Specific comments

7-5 l1 6-17: Better wording is "…. aggregation depends on source of exposure…."

7-6 Discussion of Sheppard: This paper focused on non-reactive pollutants. An additional assumption that there is no temporal structure introduced by chemical reactivity is needed to apply the conclusions to O_3.

7-6 l 13: Substitute “across” for “for”

7-7 ll 29-31: Are estimates of variability also available?

7-8 l 7: I’m not convinced that the attenuated RR estimates are conservative “from a testing point of view”. The test will be valid when the estimate and its standard error are similarly scaled, even when the estimate is biased.

7-9 ll 29-30: Please verify that Schildcrout and Heagerty stated that the standard error is necessarily larger than for a single day lag. Since the variance of a sum is the sum of the variances plus all the covariance terms, this statement is likely but not necessarily true. It won’t be true when the covariances are negative and large enough.

7-9 to 10 ll 30-1, 1-4: I think it is safe to assume the most reasonable unknown underlying health model has a distributed lag. The question then becomes the relative value of fitting a distributed lag model versus a single lag model. These models are different and capture different information in the underlying model. I think the focus should be on the usefulness of different models rather than their correctness.

7-9 l 6: Replace “may” with “will”. It will be necessary to assume an underlying true model and to know the autocorrelation structure of the exposure series in order to compare the parameters estimated from the single versus multiple day lag models.

7-12 l. 26: Add “and is not identifiable from the data”

7-14 l 6: The alternate approach assumes that all effects in the model that aren’t specified to be season-specific don’t vary seasonally.

7-15 l 2: add “and interpretation” at the end of the sentence.

7-15 l 11: Remind the reader what α means or refer to the page in the document where it is treated in more detail.

7-15 section heading: Shouldn’t this replace “from” with “and”

7-15 l. 31: replace “due” with “after”

7-16 l. 7: reword to state “…. significant when the null hypothesis is true will be greater ….” L. 8: Technically all traditional statistical inference is conditional on the null hypothesis being true, and thus provides no evidence for or against the null hypothesis (which would be a probability statement about the hypothesis directly or about the hypothesis conditional on the data). I suggest dropping the second half of the sentence on this line. L. 9: If this must be left, please reword to replace “may be of great value” to “has its place”. L. 10: Recognize that with multiple a priori hypotheses all tested at the $\alpha=0.5$ level, the overall type I error will be larger. Consider recommending a correction for multiple testing when multiple a priori hypotheses are to be entertained.

7-16 L. 23: Koop and Tole is a lousy paper and should be mentioned with reservation (and explicitly recognizing its many limitations), or dropped. An alternative if it is to be mentioned is to discuss it in the annex (perhaps it is there and I just missed it?) with sufficient evaluative commentary about its limitations.

7-35 Figure 7-1: Good separation of single vs. multiday lags helps remind the reader that these are different models being fit. Enhancing the caption to affirm this distinction won't hurt, perhaps by adding the word "distinct" before "multiday"

7-38 Figure 7-3: The single and multiple lag models estimates are displayed on the same figure without distinction, implying that they estimate the same quantities, which they don't.

7-38 and Figure 7-4: I checked the presentation of the Mortimer et al. (2002) paper, and the detail is insufficient to assure that the following comment is correct. However, it appears that the "all cities" analysis is an estimate of the effect on PEF from all sources of variation in O_3, while the "city stratified" analysis is the average of the within-city effects on PEF. Since the city stratified uses less information about exposure, it will be more variable. Also note on line 12 that the distribution functions are for the 1 to 5 day cumulative lag in each city.

7-39 l. 3: This sentence can be improved. My understanding is that the all-cities and city-specific analyses both use the same number of subjects, they just use the subjects differently and don't include all the variability in exposure.

7-45 and Figure 7-7: Same comments as for figure 7-4.

7-55 l.4-5: I don't understand why the case-crossover design and the conditional analysis would have led to stronger associations. This is worth understanding better, particularly since two different analyses from the same study appear to lead to different conclusions.

7-55 l. 27-29: The Peters study is problematic at least in part because of the unidirectional referent selection approach which is subject to an unknown degree of overlap bias (this is estimable from the exposure series alone). (Please add this limitation to the Annex summary of the paper. All case-crossover studies that don't use time-stratified referent selection have the potential to have overlap bias, so this comment can be added to all of them. See Janes et al (2005) in the November issue of Epidemiology and the commentary in the same issue by Mittleman for more perspective about referent selection in air pollution case-crossover studies.) Also a much larger study of acute MI in Seattle WA, done to replicate the Peters et al findings for PM, found absolutely no PM effect. O_3 was not evaluated in that study so it can't be added to this document, but I suspect the Peters results will not replicate in Seattle.

7-68 and Figure 7-11: Same comments as for Figure 7-3.

7-80 and Figure 7-17: Same comments as for Figure 7-3.

7-96 ll 22-28 needs revision to reflect that single and multiday lag models are different models.

7-97: Revisions to the CHS presentation are needed as given by other reviewers.

7-129: While I agree that it makes more sense to focus analyses of O_3 effects on the warm season, I find it difficult to infer that finding larger O_3 effects in the warm season is consistent with causal effects. I think it is reasonable to use warm season effects to derive quantitative relationships merely because the attenuation of concentration to ambient exposure is likely to be much less in the warm season.

7-138 l 1: Consider using the word "representative" in place of "accurate". Lines 3-4: Different population behaviors in summer and other seasons will also affect this relationship.

7-141 l 16-17: I don't understand this statement.

7-143 l. 14: There is insufficient information in the annex about the Hoppe study to make sense of this discussion.

AX7-117 l 4: replace "sample estimate" with "population mean" and insert "sample" before "mean on line 6.

AX7-118 l 3-5: it is important to recognize that there may not be enough information to determine whether the heterogeneity distribution is normal or not, regardless of what the summary density looks like.

AX7-119 l 6-8: Wording implies *h* should vary by study. Final sentence unclear.

AX7-122 l 1-2: Unclear

AX7-122 Figure AX7-1: Why is the summary density curve multiplied by 7?

Other miscellaneous comments based on the meeting discussion:

Ch 8 Executive summary: Ideally the bullets include the level or range of levels of O_3 at which each point pertains. They will also reference back to sections of the main document and/or the annex.

Ch 9: Here, or more likely in the staff paper, there should be a data analysis presented that compares the paired estimates (one pair for each O_3 monitor) of a standard based on human health with one that best captures vegetation exposure. These paired data can then be summarized in various ways (e.g. scatterplots, maps, tables). Such an analysis will be give good insight into how well the human standard works for vegetation and how comparable the two are across all geographic areas.

Dr. Frank Speizer

Comments on Chapter 7 of CD for Ozone
Submitted by Frank E. Speizer, CASAC member

General Comment: This chapter is greatly improved from the previous draft and now presents a well formulate and logical progression of summarizing the available data. The format of moving through a summary of the 1996 data followed by the update of new studies and the break down of morbidity and mortality by total, disease, and specific risk categories works. The concluding section, which should be carried over in large part to chapter 8, presents a well-documented summary of the data contained in the text and in the Annex tables.

Specific Comments:

Page 7-3, line 7: suggest add cross sectional studies to this list of studies. There are perhaps more of these than prospective cohort studies.

Page 7-5, line 17, minor point. Document starts out by saying on Page 7-2, line 25 that new studies through Dec. 2004 publications, but reference here is to Sheppard, **2005**. And it is used as bases of next couple of paragraphs.

Page 7-9, line 24: Ditto Schildcrout and Heagerty (2005) and references line 25, 26 on page 7-10. Clearly the issue of the 2005 data throughout section 7.1.3 suggest that page 7.2, line 25 needs to change to sometime in 2005.

Section 7.3 does a good job of summarizing most of the methodological issues that need to be considered. It might be worth a concluding paragraph that summarizes the issues considered.

Page 7-20, lines 10-24: It is not clear in this paragraph whether it is written as an instruction to the writer of the chapter as to what to include or the reader as to how to interpret what is to be presented. It may become clear as one moves through the various sections that the weighting of each study is or is not being presented but to put this here is confusing.

To end of section on page 7-41. In discussing the acute changes in pulmonary function (FEV or PEF) it would be useful up front for the novice reader to indicate that the normal diurnal variation of p.f. is to increase in the afternoon. This would explain why in many of the studies the afternoon values per exposure dose on the day of measurement (lag 0) does not decrease as much as the morning measurements from exposure dose on lag 1. I believe in many of the early studies there are references to these phenomena.

Page 7-69, Figure and conclusion, on unscheduled hospital admissions for respiratory illnesses is reasonably conservative in that the consistency of the findings, particularly in the climates in which changes in O3 might actually reach 40ppb do show relatively consistent results of 5-25%

increases in admission. However, the outer extreme (25%) seems rather extreme and must be considered with greater uncertainty.

Figures 7.8-7.13 There is some difficulty in comparing these figures to the annex tables in that the figures seem to oversimplify the results. For example in figure 7.13 the Chang study from Taipei suggest about a 36% excess risk in summer and 14% increase in the winter for a so-called standardized change in pollution levels. However the table suggests about half these levels for a realistic change in pollution levels would be a better estimate. Further more the figure is misleading in that it does not take into account the what happens if one considers a two pollution model in which (as would be expected) by taking PM into account the winter effect goes away. I am afraid in an attempt to simplify the text and main body of the CD important points are being left out, and only the reader who goes over the annex can sought it out. Suggest at least reference to the complexity be mention in text or a few examples be brought into text.

Section discussing specific disease risk for subsequent mortality I found it difficult to match up the results reported in text with the Annex tables. This would go much easier if there were more direct referral to the appropriate annex tables in each section of the text, rather than the intro referral to the annex tables.

Page 7-96, point one. An additional explanation for difference might be differences between populations. In fact, although there are inconsistencies the fact that the results are as consistent as they are is remarkable, given the differences noted as well as differences between populations.

Page 7-96, sentence lines 37-39. Suggest this be left out as previous sentence really summarizes the problem and the suggestion that asthmatics were found to be at greater risk is really subject to small numbers associated with a very small risk of mortality overall.

Page 7-106, paragraph 1: I think this conclusion of previous few pages comes across more negative than the data indicate. For the most part what is reported is most consistent with an adverse effect of chronic exposure on both children and young adults. To suggest that it is negative seems out of line.
Suggest soften the negative tone.

Page 7-114, first paragraph: The last half of this should be left out. Certainly there are a small number of studies, and the even smaller number of cases that contribute to the uncertainty. However, the gender difference could easily be explained by exposure differences (indoor/outdoor, and work load), and the fact that not seen in other mortality data is irrelevant.

Page 7-115, 1st bullet of summary. I take issue with suggestion that all results reported could be transient. The young adult data from the college students suggests differences in pulmonary function levels. These are important and from what we know about maximal obtained lung function are an important risk factor for the development of significant lung disease in later life. Suggest soften the negative tone of this bullet.

Page 7-136, line 6: Loose language. Although a reasonable argument is presented it is not clear that this sentence should end with "concern remains". Suggest spell out concerns or simple leave out.

Comments on Chapter 8, Revised CD Ozone

Submitted by Frank E. Speizer

General Comment: This chapter does an excellent job of attempting to pull together the major finding of the CD and attempts to provide a synthesis of the data, with a summary of the findings. The major fault seems to me to be a somewhat overbearing effort to make all the data fit together in a mechanistic interpretation, where there are too many gaps (and are likely to remain gaps) in having appropriate data. There are never likely to be long term studies in animals to provide the clues necessary to make the interpretive jump from animals to humans. Terminal experiments in six month old rats will never completely model lifelong exposure in humans. It is a great step forward that some follow up studies are being done in animals, but still that is a long way from the questions about repeated and interrupted exposures in humans. We all admit that understanding mechanism is important, but it cannot be pushed as the only way to understand the potential health impacts that must be acted upon by public health policy and that policy cannot be held hostage to whether there is complete understanding of the mechanistic pathway. It seems far worse to have the discussion bough down in discussions of completing mechanisms.

Specific Comments:

Page 8-10, line 14: Suggest spell out N. C.

Page 8-24, line 30,31: Suggest take out dashes before numbers. It suggests negative numbers when these are percent showing an effect.

Page8- 29, line 25, Referencing a little inconsistent. This particular extensive study should be referenced here.

Page 8-30, Line 22: Suggest spell out CAR first time. I suspect talking about Conducting Airways but really can't be sure.

Page 8-31, line 17. The logic does not quite follow. The studies being described are in rodents and it is enough to say that changes seem to be chronic in airways, without suggesting in this sentence that the results apply to humans. That is what is documented in the next couple of sentences.

Page 8-34, Figure 8-4. As presented is rather confusing. Since shaded area is the result of air exposure could leave off individual air plot and simply show the ozone plots. This visually would make figure easier to interpret.

Page 8-47, Figure 8.5; The text and figure essentially repeat what is in Chapter7. I would have thought in the interpretive chapter that some weighting of the studies would be discussed to assess the relative value of the studies being presented. Obviously a study involving multiple cities over multiple years carried out by one investigator should be considered to carry more weight than a single city for a short period. Without going back to the Annex to Chapter 7 one cannot get this from here. One might argue that this discussion should be in the staff paper, but then why have an interpretive chapter in the CD at all?

Page 8-60, Table 8.1 The problem with using Inspiratory Capacity is that it is generally not measured in humans. What is generally measure in Forced Vital Capacity (FVC) and because of the difficulty in taking a deep breath (because it hurts a full inspiration it is this that is reduced. I think it would be accurate to use FVC in table rather than IC. Ditto semantic issue related to airways responsiveness. Probably should use airways resistance or total lung resistance rather than lung resistance, which is not directly being measured. Under susceptibility polymorphisms not discussed. Under cardiovascular need to define ANF and PAF

Page 8-61, figure 8.9. I would defer to others more familiar with the details but the lines and arrows in this figure suggest to me that we know more that I thought we know. The data may be fairly accurate for controlled animal studies but even in the human controlled studies the indications of timing is in part the result of the experimental design. (E.g. we simply do not have enough studies that have repeated measures continuous over time to say that there are limits as suggested. My feeling would be to leave this out or put in a lot more dotted lines to indicate uncertainty. (See discussion on top of page 8-63).

Section 8.5 and 8.6
These sections might need to be revisited. They are an attempt to provide mechanisms for injuries that in themselves are poorly understood, and in large part provide arguments for greater uncertainty rather than clarity. I found myself wondering if it pushing to try to accomplish something that at this stage is not needed. The findings from the animal and human studies are what they are. (We know that smoking causes lung cancer, we do not know every step in the cellular process of exposure to injury and development of a tumor cell). To try to complete this cycle with regard to ozone injury as part of this chapter seems overreaching.

Dr. James Ultman

Review of Air Quality Criteria for Ozone (Second External Review Draft)
James Ultman

Chapter 4. Dosimetry of Ozone in the Respiratory Tract

The addition of a discussion on the principles of dosimetry has improved this chapter.

Although dosimetry has been adequately defined in the first paragraph on page 4.2, I believe that more discussion is needed to place dosimetry in the context of the entire toxicological process—exposure to dose to bioavailability to tissue damage. Exposure-to-dose refers to the transformation between inhaled ozone and the distribution of ozone uptake in the respiratory system. Dose-to-bioavailability refers to the amount of ozone and its toxic reaction products that actually reach sensitive tissue once ozone has been absorbed. Bioavailability-to-damage implies that individuals have different inherent sensitivities to ozone even after bioavailability has been completely accounted for.

In addition, there are two important technical issues that have not been sufficiently addressed in this chapter.

- What are the sites of tissue damage by ozone? Early work reported remodeling of epithelium in the proximal alveolar region and damage to ciliated cells in the large airways. Recent work indicates that cell cytotoxicity in conducting airways appears immediately downstream of branch points in an asymmetric fashion (Joad *et al.* Tox. Appl. Pharmacol. 169:26-32, 20000). Since a frequent test of the plausibility of dosimetry is whether or not they predict the correct damage sites, I feel that a brief integrative summary of what we know about focal sites of O_3 injury would be appropriate in this chapter (See also my comments on Annex AX-4).
- What are the chemical reaction kinetics and rate constants appropriate for predicting sites of epithelial cell damage when modeling ozone dosimetry? Without proper knowledge of this, serious misjudgments will be made. For example, more than 10 years ago, Pryor (Free Rad. Biol. Med. 12, 83-88,1984) hypothesized that a cascade of ozonation products was responsible for cell damage rather than ozone itself. To support this argument, Pryor presented a simple model of reaction-diffusion through a 0.1 μm thick mucous layer. By assuming that glutathione was the major ozonated species, the model predicted that virtually no unreacted ozone could penetrate to the epithelial cells. A year later, Miller et al (Tox. Appl. Pharm. 79:11-27, 1985) published a more sophisticated model that accounted for convection-diffusion in the airways with simultaneous reaction-diffusion occurring through the surrounding mucous layer. Based on their assumption that PUFA were the major ozonated species, this model predicted that ozone can reach the epithelial cells in the proximal alveolar region where mucous is at least 0.1 μm thick. The reason for this discrepancy was that the quasi-first order reaction rate constant that Prior estimated for glutathione was thousand times the rate constant estimated by Miller to PUFA. It is important that this be pointed out in this

chapter so that the reader understands that, given our present state of knowledge, we cannot say to what degree ozone itself or toxic reaction products of ozone cause epithelial cell damage.

Page	Line	Comment
4-2	18-20	A somewhat more complete explanation of airway anatomy and the corresponding differences in antioxidant profiles is important here. The respiratory system is divided into the upper airways (nose and mouth), lower airways and respiratory airspaces. Uric acid is the major antioxidant in nasal ELF, ascorbic acid and glutathione are the major antioxidants in lower airway ELF. The mouth and the respiratory airspaces do not contain a complement of low molecular weight antioxidants. PUFA probably makes a significant contribution to ozone reaction in the entire ELF except in the mouth.
4-2	27-28	By the definitions given for PAR and CAR, they are identical.
4-4	28	Modify to read "…concentration of O_3 at a predetermined time during inspiration."
4-5	8	Remove extraneous "to"
4-5	9	Add sentence: "…differences in V_D. In particular, they concluded that the intrinsic mass transfer parameter (Ka), was proportional to the ratio of the respiratory flow to V_D. In a subsequent…"
4-6	1	Modify sentence: "…with the volume of the lower conducting airways…"
4-6	3&5	"Ka" not "K_a.
4-6	15	"1 L/s" not "1 mL/s"
4-6	20	Modify sentence: "…volume of the lower conducting airways…"
4-6	21	Modify and add sentence: " …p=0.001). The better correlation found by subtracting off the upper airways from V_D can be explained by the fact that very little ozone is absorbed in the upper airways during oral breathing at 1 L/s. Both $V_{P50\%}$ and lower airway volume were greater in males than in females. These findings…"
4-8	16-17	Modify sentence: "…In addition to measuring pre-to-post exposure changes in FEV_1, they used the peripheral bronchial cross-sectional area available for diffusion (inferred from the alveolar slope of CO_2 expirograms) as an alternative response variable. At a fixed …"
4-8	25	Modify sentence: "…with the $V_{P50\%}$ determined…"
4-10	1	It was dose distribtution (not damage!) that was modeled.
4-10	3-11	See the first bullet item above.
4-10	30-31	Here it is important to be specific about what is meant by the "dose." Is it the total uptake or uptake per unit area?
4-12	29	Modify sentence: " The finding that the efficiency of O_3 uptake…"
4-13	4	Modify sentence: "…fixed inhaled concentrations.."
4-13	8-10	This sentence is not correct. If FA is inversely related to flow, this implies that the gas phase resistance is important. If FA depends on concentration, it implies that chemical reaction in the mucous or

		tissue is important.
4-13	22-30	This complex sentence needs to be rewritten.

Annex AX4. Dosimetry of Ozone in the Respiratory Tract

The annex presents a complete collection of research (since 1996) in the areas of dosimetry experiments and modeling is complete. The annex is well-written and provides a critical evaluation of the research results. Following are my detailed comments.

Page	Line	Comment
AX4-1	16	**A serious problem in current modeling efforts is a knowledge of the reaction rate equation and its associated rate constants.** It would be useful to acknowledge this by inserting a sentence at this point. For example: "…has been resolved. Related to this issue is our lack of knowledge of the correct chemical reaction kinetics and rate constants to use in extrapolation models."
AX4-7	6	Change line to read "…intrinsic mass transfer parameter called the overall mass transfer coefficient (Ka)…" Note that the 'a' should be in-line with the K throughout the annex as well as in chapter 4.
AX4-7	9	Change line to read "…in V_D. Combining their data with those of Hu et al.(1994)…"
AX4-7	21-24	Replace by the following text:"…region. Data were analyzed by expressing the overall diffusion resistance between the respired gas and the epithelial cells as the sum of individual gas-phase and liquid-phase resistances. The liquid-phase resistance made an important contribution to the overall resistance, implying that changes in the reaction rate of ozone in ELF would cause concomitant changes in the ozone uptake. The gas-phase resistance was inversely related to the volumes of the oral and nasal cavities during oral and nasal breathing, respectively.
AX4-7	25	Replace the first phase by "Ultman et al. (2004) used separate bolus and continuous exposure sessions…"
AX4-8	9	Add the following sentence:"…distal lung. Data from the continuous exposure sessions indicated that overall ozone uptake was related to breathing pattern but was not correlated with anatomical dead space volume. Thus, these findings…"
AX4-9	1	A more accurate title would be "Overall Uptake Studies"
AX4-10	29-31	The citation of Postlethwait (2000) is appropriate, but is misleading to cite that reference alone. These investigators assayed for local cytotoxicity at specific sites along a major path along the conducting airway. They observed that cell damage was unsymmetrical distributed at branch points and that distal branches exhibited less damage than proximal branches. Earlier studies noted damage to ciliated cells in proximal airways and remodeling in the proximal alveolar region. Such information provides a critical backdrop with which to assess the plausibility of the exposure-dose-response

		paradigm. I realize that detailed material of this nature will appear in chapter 5, but I still feel that a brief summary is warranted in this chapter.
AX4-10	10	Modify line to read "…model that had asymmetrically branching…
AX4-11	27-30	These three lines do not adequately express the limitations in our knowledge of the reaction rates and reaction rate constants that underlie ozone damage. Lacking better information, virtually all mathematical models assume that the reaction rate in the liquid lining layer and in tissue is quasi first-order with respect to ozone concentration. For example, Miller et al. (Tox. Appl. Pharm. 79:11-27, 1985) assumed that quasi fisrt-order reaction of PUFA with ozone was the most important reaction to consider. They then computed the first-order rate constant by multiplying their estimate of PUFA concentration with the known second-order reaction rate constant for the ozonation of oleic acid, obtaining a value in mucous of 1198 s^{-1}. Pryor (Free Rad. Biol. Med. 12, 83-88,1984) performed an analogous computation using an estimated glutathione concentration and the second-order reaction rate constant he previously measured for the ozonation of glutathione. He obtained a much larger value for the first-order constant of 10^6 s^{-1}. Bush et al. (Tox Appl Pharm. 173:137-145, 2001) estimated the first-order constant of ozone in mucous using a different approach. By simulating bolus-response data obtained in healthy non-smokers with a single-path convection-diffusion model, they obtained a first-order rate constant of to be $8x10^6$ s^{-1}. The large differences between these reaction rate constants have serious consequences when they are used in models of ozone dosimetry. Both the uptake of ozone at the gas-mucous interface and the fraction of the uptake that reaches the epithelial cells are sensitive to the value of the reaction rate constant.
AX4-15	16	It should be pointed out that specifying mass transfer coefficients that do not depend on age is not a reasonable assumption.

Review of Air Quality Criteria for Ozone (Second External Review Draft)
James Ultman

Chapter 5. Toxicological Effects of Ozone

The authors have provided on a excellent and concise summary of the literature on this expansive subject . In making the final revision to the chapter, I believe that they should consider additional material that emerged during the panel discussion during the December meeting.

As I pointed out in my comments on chapter 4, there is a discrepancy in the literature about whether or not ozone from respired gas can penetrate the liquid lining layer and reach the epithelial cells. Pryor (Free Rad. Biol. Med. 12, 83-88,1984) presented a simple model of reaction-diffusion through a 0.1 μm thick mucous layer. By assuming that glutathione was the major ozonated species, the model predicted that virtually no unreacted ozone could penetrate to the epithelial cells. A year later, Miller et al (Tox. Appl. Pharm. 79:11-27, 1985) published a more sophisticated model that accounted for convection-diffusion in the airways with simultaneous reaction-diffusion occurring through the surrounding mucous layer. Based on their assumption that PUFA were the major ozonated species, this model predicted that ozone can reach the epithelial cells in the proximal alveolar region where mucous is at least 0.1 μm thick. The reason for this discrepancy was that the quasi-first order reaction rate constant that Prior estimated for glutathione was thousand times the rate constant estimated by Miller to PUFA.

Clearly, the extrapolation of laboratory data across species as well as to different exposure scenarios requires a better understanding of reaction kinetics and rate constants. I think that a subsection should be added under section 5.2.1 to summarize the state-of-the-art with respect to reaction kinetics and rate constants.

The previous work in this area can be divided into three categories:

1) Estimation of reaction rate constants.
   (See the Pryor and Miller articles cited above)
2) Measurement of reaction rates in nasal an bronchoalveolar lavage fluids
   (Mudway and Kelly, Free Rad. Res. 25:499-513, 1996; Housley et al. Int. J. Biochem. Cell Biol. 27:1153-1159, 1995; Mudway and Kelly. Toxicol. Appl. Pharmacol. 148:91-100, 1998)
3) Measurement of reaction rates for pure substrates and mixtures
   (Kanofsky and Sima. J. Biol. Chem. 266, 9039-9042, 1991; Kanofsky and Sima. Arch. Biochem. Biophys. 316:52-62, 1995; Pryor and Uppu. J. Biol. Chem. 268:3120-3126, 1993).

Page	Line	Specific Comments
5-2	22-23	The statement "…most likely results from its reactions with PUFAs…" should be softened to include the possibility of damage by ozone itself and other reaction products.
5-3	Fig. 5-1	Moles of oxygen do not balance between the reactants and products.
5-7	30-31	The statement "…it is unlikely that ozone reacts directly…" is unnecessary. At this time, both the possibility of direct ozone reaction and byproduct reaction should be considered.
5-9	Fig. 5-3	I really like this figure. I vote against modifying it, as someone suggested during the panel discussion.
5-13	18-19	As discussed on the top of page 5-10, reactions of ozone with AA may not always be protective.

Review of Air Quality Criteria for Ozone (Second External Review Draft)
James Ultman

Chapter 6. Controlled Human Exposure Studies

The authors are to be commended on a excellent and concise summary of the literature on this expansive subject . In making the final revision to the chapter, I believe that the authors should: 1) introduce the concept of "Haber's Law" in an explicit manner; 2) reorganize some of the existing text to provide a better focus on issues of intersubject variability that are not explained by dosimetric factors; and 3) improve their comparison between square and triangular exposure patterns.

1. Haber's Law simply states that the incidence and/or severity of a toxic effect is directly related to the total exposure (i.e., exposure concentration•time, or more correctly the time integral of the exposure concentration•time). When viewed through the prism of Haber's Law, ozone exposure-response studies exhibit several apparent consistencies. The most obvious is the fact that the relationship between response and total exposure is related to exercise level. Is it really exercise per se or is it ventilation that affects response? After all, dosimetry studies have shown that the inhaled dose (i.e., exposure concentration•ventilation rate•time) is closely related to respiratory ozone uptake. In addition, Haber's Law cannot explain the differences in lung response seen with different exposure patterns or the nonlinear effect of exposure time. I think that the concept of Haber's Law should be introduced in subsection 6.2.1 and then contrasted with the research results presented in subsections 6.2.2-6.2.4. This should be contrasted to the use of transport-based dosimetry models that can take ventilation rates and exposure patterns into account.

2. Intersubject variability is an important aspect of human subject studies aimed at protecting the most sensitive segment of the human population. A portion of this variability may be attributed to dosimetric effects such as ventilation rate, exposure pattern, and lung anatomy. However, there is also a large amount of "unexplained variability" due to innate biological sensitivity of the individuals. This is demonstrated by the empirical exposure-response model of McDonnell et al. (Am. J. Respir. Crit. Care Med. 156:715-722, 1997). This model provides a prediction of subject-averaged pre-to-post percent change in FEV_1 from the exposure concentration, ventilation rate, exposure time and age of the subjects. Even after accounting for these factors, the data on which the model is based exhibits a high degree of scatter about the mean (see fig. 1 in the McDonnell article) due to other unknown factors. I believe that the material in subsection 6.4 and 6.5 could be better organized around this theme of dosimetric effects versus other effects. This would better tie chapters 4 and 6 together.

3. The effect of exposure pattern presented on pages 6-7 and 6-8 is an important finding, and I believe that the discussion could be written in a clearer manner.

Perhaps, the most consistent point between the two previous studies is that the pre-to-post change in FEV_1 at the end of the exposure was the same at the end of both the triangular and square exposures, but the FEV_1 fell off faster during the triangular exposures so that health effects were more prolonged than during the square wave exposure. This is in direct contradiction to Haber's Law since it means that the FEV_1 response between the two exposure protocols would not collapse onto a single curve if plotted against (exposure concentration) x (exposure time). In particular, the data for the triangular exposure pattern would fall off even more quickly than the square wave pattern if plotted in this manner. Another point that is apparent from Hazucha's data but not as apparent from Adams data is that there is a peak FEV_1 decrement that occurs about an hour after the peak in exposure concentration. Thus, the triangular exposure is also capable of generating a greater instantaneous value of the FEV_1 decrement than the square wave exposure.

For these points to be perfectly clear to the reader, it would be show the comparable square wave responses in figure 6-1.

Page	Line	Specific Comments
6-6	17-19	Another reason that ventilation is often normalizing to body size or as a percent of maximum aerobic capacity is to insure the same level of relative exertion between different subjects.
6-8	15-17	Why did you choose not to comment on the results of these other two studies?
6-14	2	Do you mean "inverse correlations?"
6-14	5	Do you mean "decrement of lung function?"
6-14	6-8	I don't follow this sentence.
6-15	17-19	Was lung ventilation controlled?
6-17	8	Was exercise level the same for asthmatics and normal subjects?
6-18	17	Was exercise level the same of allergic and normal subjects?
6-19	13-15	This is an interesting result that suggests a reduced diffusing capacity of the alveolar-capillary membrane or shunting of blood between the pulmonary artery and pulmonary vein.

Review of Air Quality Criteria for Ozone (Second External Review Draft)
James Ultman

Chapter 8. Integrative Synthesis

Page	Line	Specific Comments
8-21	5	It is not clear what "controlled for dose" means. Exactly what dosimetric was used to put the dose-responses on an equal footing? Was experimental data available to make this comparison, or were extrapolation models used to make the comparison?
8-21	30-31	Concluding that the rat and human have similar sensitivities requires that dosimetric effects be isolated from innate sensitivity in a rational manner. This does not appear to have been done in reaching the conclusion given in this sentence.
8-26	27-29	Rewrite this in the following manner: "… have observed gender-specific effects in the uptake of ozone that appear to be related to breathing pattern and lung size. However, spirometric responses did not correlate well with ozone uptake alone…"
8-23	4-12	I don't quite understand what is meant under item b). I also think an item e) should be added to reflect anticipated improvement in chemical kinetic formulations of ozone-substrate reactions.
8-26	Fig 8-2	Caption should read "..have more than 5, 10,…"

Review of Air Quality Criteria for Ozone (Second External Review Draft)
James Ultman

Executive Summary-Dosimetry Studies

This section accurately captures important points regarding what is known about ozone dosimetry. It does not, however, attempt to point out what the current limitations are. I am particularly concerned that nothing is said about the chemical reaction kinetics and reaction rate constants that drive the uptake of ozone and its decomposition into potentially toxic products. Given current gaps in our knowledge of the reaction rate constants, we cannot expect to develop reliable extrapolation models. Also, concerning the seventh bullet item, I believe that it is more accurate to say that "new experimental work suggests that the conducting airways are an important site of ozone-induced cell injury in addition to the proximal alveolar and centriacinar regions." An important novelty of the recent work is the asymmetric pattern of cell damage that was observed in the vicinity of airway bifurcations (Joad et al. Tox. Appl. Pharm. 169:26-32, 2000).

Dr. Sverre Vedal

December 2005
Critique of 2nd Ozone Criteria Document draft
Sverre Vedal

Chapter 3 (focus on exposure)

page

54. line 1. Noting that some personal exposure measurements are below central ambient concentrations is misleading. Also, strong correlations are found between personal and stationary sites, but this is in populations spending time outdoors.

63-65. The values under the column heading "Indoor/Outdoor Concentrations" cannot be correct in many instances.

71. The issue of lack of correlation over time between individual personal concentrations and central concentrations, vs. reported good correlation between aggregate personal concentrations and central concentrations, is an important one. Which is most important for the interpretation of the time series studies? Is this a different manifestation of the ecologic fallacy? This needs more substantial discussion in this chapter.

Chapter 7 (Epidemiologic studies)

Bigger points.

1. In general, this chapter provides a relatively balanced presentation and interpretation of the epidemiologic findings, especially regarding effects of chronic exposures (p.106,108,109,117). Concluding sections are appropriately cautious (with the exception of that on cardiac hospitalizations). Chapter 8 (Integrative Synthesis) should takes its cue from this chapter.
2. p.101. Because the Gauderman 2004 report of the Southern California children's study is the most definitive study to date on children's lung function and long-term exposure, its findings need to be given great prominence. It is only given short shrift in this chapter.
3. The conclusion regarding associations between ozone and cardiac hospitalizations (p.74, line 1) is an overstatement. Based on Figure 7-13 (p.72), only one of two warm season studies shows an effect.

Smaller or detailed points.

Page

104. The Calderon chest x-rays findings do not directly implicate ozone. The study has other substantial problems as well.

105. The findings of the initial Berkeley study (Kunzli 1999) were not replicated in a more recent report this year (Tager 2005), at least when effect modification was not considered, as it was not in the initial report.

105. The findings of the Sherwin study, besides not being able to implicate ozone exposure, are suspect given grave concerns about the interpretation of the histologic findings.

114. The lack of an effect on lung cancer in the ACS provides substantial evidence against an association and is much more meaningful than the findings from AHSMOG on only a limited number of cases.

138. line 6. Brauer, et al. (2002) is not included in the reference list.
140. I'm not sure using shrunken effect estimates to conclude that only 2 of the 95 cities had negative effect estimates in the 95-city (Bell 2004) study is meaningful. Nevertheless, this observation cannot be compared directly to the finding in the European study (Gryparis 2004) in which many more cities had negative effects, but where effects were not shrunken.
142. How solid is the observation that there are greater PFT declines in asthmatics in controlled exposure studies?

Editorial points.
148. line12. "alveolar"should be "alveoli"

Chapter 8 (Integrative synthesis)

Bigger points.
1. Synthesis and integration vs. recapitulation.

This integrative synthesis has become too long. Just the review section (to p.58) is 15 pages longer than the entire first draft of Chapter 8, and the entire chapter is now twice as long as before. Part of the reason for this is the overly detailed review of individual study findings in several sections, findings presented in detail in earlier chapters of the CD. The review of the epidemiologic studies (pp. 41-50) is particularly guilty in this regard, as is the section on possible susceptibility risk factors (p.73, etc.). Other suggestions to reduce the length include: i) combining Tables 8-2 (p.76) and 8-3 (p.77), since they have extensive overlap, and ii) attempting to cut out repetitious portions that repeat earlier sections of even this single chapter.

Although the chapter is now overly long, there have been substantial improvements to the chapter. There is now included an attempt to provide some basis for the apparent effects on cardiovascular deaths (see below). Allergen-ozone interactions are given some play (see below).

2. Plausibility and time series studies.

I am still struck by some issues that relate to trying to support the plausibility of the epidemiologic study findings on ozone, and in particular the time series findings. Several criteria are presented that are intended to be used to assess plausibility (p.39). These are the same criteria used to assess the plausibility of PM effects, but they are not entirely adequate here. What are some other major threats to the plausibility of the epidemiologic findings as concern ozone? The criteria do not address at least two issues that, while not unique to ozone, are particularly acute in this context: the role of the peculiarities of ozone exposure, and the difficulty in adequately controlling for effects of meteorology. Both of these issues surfaced in the evaluation of PM effects, and attempting to address them helped to advance our understanding in that case. However, both are much more acute issues for ozone than for PM.

Regarding exposure, the susceptible population for the effects of short-term ozone exposure on mortality is likely a somewhat unusual population in terms of level of activity and time spent outdoors, and possibly the presence of underlying disease, all of which might serve to reduce exposure to ozone, i.e., this is a population that is at the low tail of the ozone exposure distribution. While one cannot claim that such dire effects of ozone at very low levels of exposure are inconceivable, they do not strike me as likely. Regardless, this issue should be

front and center in a discussion of the plausibility of the epidemiologic findings, at least for mortality.

A related exposure issue is the relevance of ambient monitors to exposure. If we think back to the case of PM, compelling data were reported that indicated that exposures to the gaseous pollutants, including ozone, did not correlate with ambient concentrations. This motivated a controversial argument that the gaseous pollutants should not be considered confounders of the time series PM-health effect associations. Exposure issues should be central to any integrated synthesis, and particularly so for ozone, but they are almost entirely absent here in the discussion of plausibility. Instead, selections from the Hill criteria are trotted out once more, and are again misused (see below).

Second, changes in ozone concentrations, more so than for any other criteria pollutant, are directly related to changes in meteorology. The relatively simple specification of meteorology in the models used in time series studies seems unlikely to allow the effects of ozone itself to be disentangled from those of meteorology. Seasonal stratification, as suggested (p.54, line 5), while important, is not adequate. Confounding of the ozone effects by meteorology is therefore still a real possibility in the time series studies.

I must again point out some issues in the use of the Hill criteria to assess causality (p.39). Temporality does not refer to lag structure, but rather to the exposure preceding the effect. To assess this, we should evaluate negative lag effects (the exposure following the effect by one or more days), but this is not done. The criterion of temporality is therefore not met, since it is not addressed. Discussion of coherence is mixed up with plausibility, but these criteria are admittedly sometimes difficult to distinguish. The strength of an association can have nothing to do with its statistical significance (p.51); they are only related through the fact that strong effects are more likely to be statistically significant than weak ones. However, strength is a direct function of the size of the effect estimate, not its statistical significance. Air pollution effect estimates in air pollution epidemiology are uniformly weak because the sizes of effect estimates are small, especially those obtained from time series studies. The criterion of strength of association can therefore not be used to provide support for causality in this case.

Finally, I am struck by findings, probably best summarized by Stieb D, et al. (J Air Waste Manage Assoc, 2003) in his meta-analysis of time series studies of all of the criteria pollutants, save lead, showing that any pollutant of interest can be shown to be acutely associated with mortality using a time series design in a substantial majority of studies. How many times can we continue to claim that every pollutant that we examine in this way has very similar effects on mortality? Although it is conceivable, I would argue that each is unlikely to have such similar effects. Should we not consider whether there is something problematic in using the time series design for this purpose? At best, in my opinion, findings on all of the criteria pollutants using the time series design indicate that there is something in the air pollution-meteorology mix that affects mortality. Findings from time series studies, then, do not seem to provide a very compelling basis for establishing policy on <u>individual</u> pollutants.

3. Cardiovascular effects.

The presentation of experimental findings to support the plausibility of cardiovascular effects of ozone is much more substantial than in the first draft (see especially p.38 and on), and is welcomed. The appropriation of findings relating to widening of the alveolar-arterial oxygen gradient and V/Q mismatch (mentioned in several places) to support an argument for cardiovascular effects of ozone may be a bit of a stretch, however. Neither necessarily reflects a

pulmonary vascular problem, although they might. It is just as likely (arguably more likely) that these instead reflect airways effects or effects in the alveoli, which are much better documented. Perhaps the point is that these effects can in turn have effects on the heart. If so, that needs to be made clearer. Also, note the human experimental findings of Gong H, et al. (Am J RespCrit Care Med, 1998), in which no major cardiac effects were found, but which nevertheless found increased myocardial work and heart rate with ozone exposure. Given the paucity of experimental data, all such relevant information should probably be included in an integrating discussion.

The uncritical presentation of epidemiologic findings on cardiovascular endpoints (p.45, for example), to be taken at face value, is not useful in an integrative synthesis (see comments on time series studies, above). The presentation can also get one-sided; for example, I find no suggestive evidence for associations with cardiovascular hospitalizations (Figure 8-5 [D], p.47) as opposed to what is stated (p.48 [line 13]; p.67 [line 6]; p.68 [line 12]). The absence of associations relating to cardiovascular hospitalizations is puzzling and should be brought out in the context of coherence, in this case providing some evidence against it, at least based on studies available to date.

4. Chronic effects.

Evidence for the presence of chronic effects of ozone based on epidemiologic studies is consistently overstated. Concluding statements in Chapter 7 are more on the mark. In the Southern California children's study, arguably the most rigorous study of its kind, ozone was the only pollutant for which no effect was found on attained level of lung function after 8 years of follow-up. In the ACS study, reporting of the ozone effect was given little prominence – it was tucked away in one table in the 2002 JAMA paper and consisted of an almost statistically significant effect using warm season ozone as the exposure metric, and no effect when full year ozone was used. No effect on mortality was seen in the AHSMOG study. Similarly, no association was observed in the recent study using ACS data in Los Angeles (Jerrett, 2005) in which ozone concentrations were modeled over a relatively small area (urban vs. national). The statement, "associations have been reported between long-term exposure to O_3 and increased morbidity; development of respiratory disease; and declines in lung function and lung function growth" (p.40, line 11), while possibly technically correct (i.e., "have been reported"), in no way reflects the weight of evidence that should be presented in an integrative synthesis.

5. Threshold.

Perhaps the most compelling epidemiologic evidence for the presence of a threshold is the relatively consistent finding of warm season effects, but no cold season effects.

6. Allergen-ozone interaction.

It is good to see a discussion of this interaction included in this draft (p.29, 67, 85 [line 4]). I don't find the human experimental findings quite as convincing as portrayed: the findings of the initial study (Molfino N, et al. Lancet, 1991) could not be replicated by either another group (Ball BA, et al. JACI, 1996), or even the same group (Hanania NA, et al. Chest, 1998), the latter two reports not referenced in the main chapters of the CD, either here in Ch. 8 or in Ch 6, but they are referenced in the Annex to Ch.6.

7. Consistency with Chapter 7 (Epidemiologic studies).

There are many instances in this synthesis chapter where conclusions are overstated in contrast to those presented in Chapter 7. Better coordination between the two chapters is needed.

Smaller or detailed points.

Page

12-18. Consider whether verbatim recapitulation of 1996 conclusions over 5 pages is needed.

19. Is "confounders" what is meant here in the context of experimental studies?

22. The effects of nasal breathing and increased airflow on uptake seem counterintuitive, but could perhaps be clarified with clearer wording.

23. Human studies are included under this heading of "Toxicological effects."

24. In this section on pulmonary function (8.4.2.4.1), there is no mention in the context of effects on FEV1 and FVC that these are predominantly due to reductions in inspiratory capacity (IC). Effects on IC are mentioned in several places, but the presentation here makes it appear that this effect is different from the effect on FEV1 and FVC, which it is largely not.

41. Insistence on the consistency of findings can get to be ridiculous, at times. For example, what is the meaning of "…but consistent positive associations … have also been observed" (p.41, line 6) as a qualifier of a statement that morbidity effects "…have greater variability…"?

50. Are there data suggesting that severe asthmatics are more susceptible to ozone mortality effects (line 14)?

54 (section 8.4.3.2.3). I would also point out that there is generally less correlation between ozone and the co-pollutants, facilitating analytic control of co-pollutant confounding, as opposed to for PM where correlations tend to be strong.

56. line 7. The contention that ozone concentrations tend to be spatially variable in urban areas is sort of true; however, the variability tends to be much less than for most pollutants.

58. line 25. I was puzzled as to why lung function was not considered as a morbidity endpoint, but perhaps the coherence with the experimental work is too obvious, and so it was felt to be unnecessary in this discussion.

60 (table 1). This table is a little incomplete. The cardiac endpoints from Gong, et al. should be added to the human exposure column. Also, see comments above on appropriateness of using O_2 transfer and V/Q mismatch findings.

Fig 8-9, p.61 is confusing. Make clearer what the different arrows signify.

66. line 4. Could be clearer here on what is meant by the point that baseline lung function is lower in the elderly, in the context of decreased sensitivity to ozone with increasing age.

67. line 6. Cardiovascular hospitalization studies are inconclusive, as noted earlier in the chapter, and shown in Table 8.5

68. line 12. As stated above, there is little indication from Table 8.5 for cardiovascular hospitalizations. I would instead support this discussion with newer findings from observational studies on HRV cited earlier in this chapter.

69. line 5. This statement on chronic effects on lung function, mortality, lung cancer and asthma is a clear overstatement. Note, the university studies (Yale, Berkeley) are not longitudinal in design, but rather cross-sectional.

70-71. This section contains appropriately qualified statements on the mechanistic basis for cardiac mortality effects.

79. table 8-4. What is the column "Cases ($x10^6$)"? Is it annual incidence, or some other measure of prevalence? If the latter, how does it correspond to the percentage prevalences in the other columns? Clarification is needed.
81. There is no attempt to cast a critical eye to the intervention study results: asthma hospitalizations in Olympics Atlanta 1996 and California 1998 [Neidell MJ, 2004]. In the latter study, it was concluded, in fact, that there was no effect of ozone on admissions, as opposed to for CO.
84. line 8. It is unclear how meta-analyses on the influence of season "suggest a causal association" in the mortality studies.
87. This integrative synthesis chapter ends with a whimper. The concluding bullets are not nearly as helpful as they might be.

Editorial points.
53. line 24. Should be Schwartz 2005, not 2004.
65. sentence editing needed: lines 19 and 30.
83. line 28. replace "field" with "epidemiologic"

Dr. James (Jim) Zidek

Revised Comments of the Draft Ozone AQCD (2nd External Review Draft)
Chapter 3
James V Zidek, December 9, 2005

CHARGE QUESTIONS

CHARGE QUESTIONS-OVERALL

Volume I is a good digest of the technical material for the general readership. However for my review, the arrangement used in the 1st External Review Draft would have been preferable. In fact, I printed out hard copies of Chapter 3 and its appendices so I could put them back together.

CHARGE QUESTIONS-EXECUTIVE

Overall the summary of Chapter 3 is well written and comprehensive. It communicates that material well. However, in my complementary set of detailed comments about the 2nd Draft, I re-state concerns about the 1st Draft about the CTM model- and kriged-estimates, that are not reflected in the revision or Summary. Furthermore, the claim in last bullet on E-8 about "surrogate measures for aggregate personal exposures" seems surprising. I would have thought the ambient monitoring measurements would overestimate personal exposures as well fail to explain their variability.

> **CHARGE QUESTIONS – CHAPTERS 2 & 3.** Given the expanded information related to "other photochemical oxidants" in response to earlier CASAC advice, what are the Panel members' views with regard to the scope and scientific adequacy of Chapters 2 & 3? Are there any other important topics that should be addressed?

My detailed comments cover topics that need to be addressed. In summary, the main points:

1. **"Correlation" seems to be used in both a technical and non-technical way and that can mislead the reader. The report does not recognize that correlation is not the most appropriate measure of dependence for the non-Gaussian fields considered. Even in the Gaussian case, two highly correlated sites may be quite different, a fact that is not explicitly recognized.**

2. **More analysis of the fields of extremes of the sort used to state regulatory criteria such as the 2nd largest annual daily concentration is needed.**

3. **Improved spatial maps and contour plots of the ozone field could have been made using more modern spatial prediction methods, in particular, ones that incorporate time as well as space. Moreover, the possibly severe underestimation of uncertainty in these maps due to the use of kriging is not acknowledged.**

4. **The report offers no indication of the size of error and bias made in estimating the PRB level, in particular using the CTM.**

5. **With respect to APEX, no evidence is provided that it actually forecasts personal exposures accurately enough for it to serve its intended role. No uncertainty estimates are given for its exposure predictions nor is anything said about its sensitivity to its model parameters whose distributions are estimated from available data.**

GENERAL COMMENTS

1. The phrases “O3 concentrations”, “observed O3 concentrations” and “O3” are used at various points to mean the same thing, “measured O3 concentrations”. In fact “ozone concentrations” are never observed and at best only measured with error at monitoring sites. At the very least, the terminology used should be made uniform, “measured O3 concentrations”, being the most accurate. For expediency, a caveat near the beginning of the chapter might assert that these three phrases mean, “measured O3 concentrations”.

2. “Correlation” is used in two senses. The first is technical, the degree to which one variable can be linearly predicted from the other with which it is correlated. The second is casual, meaning dependent or associated. In fact, in the detailed comments below an example is given where the two variables have fairly exact curvilinear relationship so that one is predictable from the other but where they are not (strongly) correlated in the first sense. To avoid misunderstanding, “correlation” should be not be used in the second sense when lots of other good words exist to cover the relationships being described.

3. Even when used in the technically correct fashion, “correlation” tells only part of the story. Two highly correlated sites can be very different as we see in the hypothetical example presented in Figure 1 below.

4. At a more substantive level, “correlation” is inappropriate as a measure the association between “extreme values”, that is, statistics like 95th percentiles or the 4th largest annual maximum 8-hr measured concentration. Other ways of measuring dependence for such statistics should be used. (See for example, Ledford and Tawn (1996).)

5. Although criteria metrics like 4th and 2nd largest daily maximum measured concentrations, for example, are the fundamental to regulatory policy, the AQCD gives them only passing reference. Yet for policy-making, knowledge of their spatial properties is important. In particular, my analysis (for ozone using the AIRS database) for the First Draft indicated that the intersite dependence for these metrics can be quite weak even when that of the spatial concentration field is quite strong. In other words, in spite of large intersite correlations the monitoring networks for some urban areas may not be sufficiently dense as to make compliance at the monitors sufficient to predict with some confidence compliance at locations between. A more thorough investigation of the properties of such metrics would have been desirable to provide a basis for assessing the efficacy of standards that might eventually be developed on the basis of the AQCD.

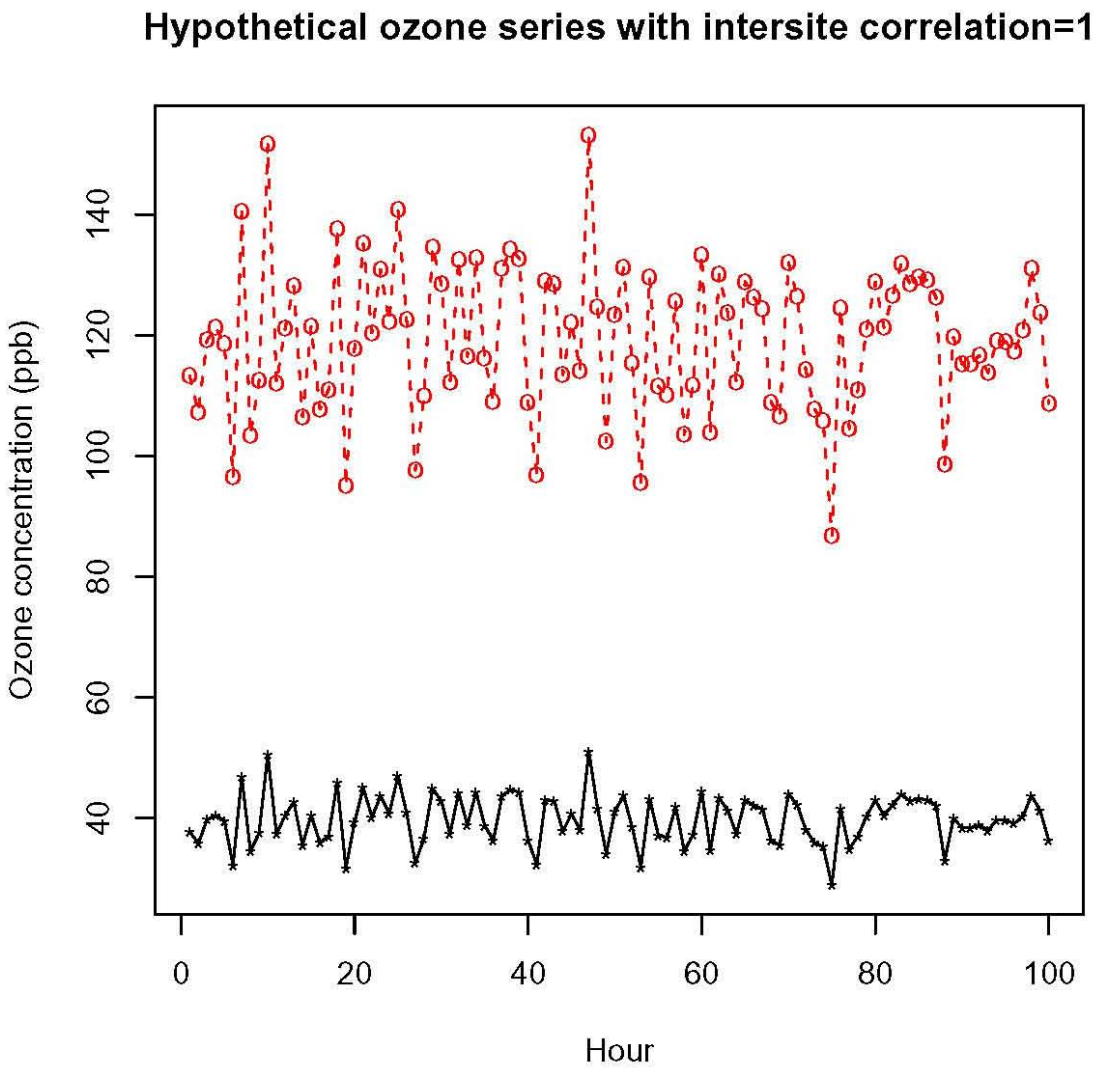

Figure 1. This figure shows the time series of measured hourly ozone concentrations at two hypothetical sites. Although they are very different, the series are perfectly correlated with Pearson's r = 1.

6. Both ppb and ppm units are used in the document. For uniformity one of these should be adopted. The preferred option would be ppb for a number of reasons. For one thing, 0.120 ppm just does not look like a serious ozone exposure – the small number makes it seem insignificant. More importantly, tables and axes on graphs would be simplified by the resulting reduction of "clutter" in the reader's field of vision. In fact the left hand most "0" in say "0.081" is there merely for "window dressing"- it has no other purpose. The second "0" is mainly a "placeholder" but like the first, conveys little other information. In contrast tables and graphs based on ppb would appear simpler and hence make it easier for the reader to grasp their intended message.

7. Captions with boxplots do in some cases say what they must, that “the boxes indicate the interquartile range and the whiskers, the largest and smallest values” or whatever is appropriate. However, a great many of those captions miss that phrase at the risk of confusion since practices for boxplots are not completely standard.

8. “Percentile distribution” is used frequently when in reality “distribution” seems to be intended, since the variable being represented is not a percentile but rather a concentration. This comment applies to the text as well as some of the graphs. In the case of one table at least, percentile distribution is correct.

9. Comments were made about Section 3.7 & AX3.9 in the first draft. On the whole it is very well written. Moreover, it does solve the problem presented by by important responses that cannot be measured but needed to characterize the PRB concentrations.

   The two particular concerns arise in connection with respect to that solution. The first is the use of the outdated kriging method for mapping the spatial field (addressed above in the general comments). The second is the use of CTM deterministic models to simulate unmeasured responses. Generally the latter are called “simulated data” to make it absolutely clear that these are not real data in any sense. (The authors here refer to them as “model data”.) However, such simulated data are not measurements. To quote the much cited paper of Oreskes *et al.* (1994):

   A model, like a novel, may resonate with nature, but it is not a “real thing.

   One way of used to validate such models consists of using the model to predict responses that have been measured and comparing the simulated and real data. A good fit tends to confirm the assumptions. Even that kind of assessment has been challenged. Again quoting Oreskes *et al.* (1994)

   To do so is to commit a logical fallacy, the fallacy of “affirming the consequent.”

   Nevertheless, one might well trust in the predictive value of a model that got a good pass on such a confirmatory test. Moreover, the Report does present results, in particular through plots, showing that the predictions generally track the data. Yet little analysis of these results is given. In particular, they do not quantify two important features of those predictions, their bias and their accuracy, as predictors of the unmeasured concentrations.

   As noted in our first draft comments, the bias, which varies by region and hour of the

   day, can be quite large. In fact, calculations reported in our earlier comments are

   broadly in accord with those reported in the paper of Arunachalam et al (2001).

They compare the MAQSIP and CMAQ models and find the following for ozone during the period in their study based on model outputs for 12km sq grid cells:

Period	Bias		Error	
	CMAQ (ppb)	MAQSIP (ppb)	CMAQ(ppb)	MAQSIP (ppb)
0900-1000	11	14	12	15
1000-1100	10	9	14	12
1100-1200	14	13	16	16
1200-1300	21	21	22	22
1300-1400	5	3	8	8
1400-1500	2	-2	8	9
1500-1600	6	2	11	10
1600-1700	16	11	16	13

Table 1. Bias and Error in the prediction of hourly ozone concentrations by two deterministic data simulators for North Carolina during the summer of 1996.

This leads us to wonder about the meaning of the claim on page AX3-146: ”These models can simulate most of the observed variability in O3 and related species.” Is simulating variability different than simulating level to which the table above and our earlier comments apply?

Arunachalam et al. (2001) conclude: “While both models overpredict the observed values, the bias and gross error are higher in CMAQ than MAQSIP. For the photochemical daytime period (between 9:00 a.m. an 5:00 p.m.), however, when the models are expected to have peak photochemical activity, both MAWSIP and CMAQ predicted means are quite comparable, with some slight differences on a day-to-day basis.” The latter at least is reassuring.

The simulated data are compared with data in Figure AX3-82 albeit at a monthly level which washes out short term differences. At this resolution, the CTM output overestimates the data in the eastern United States, at least in 2001. That is broadly consistent with the findings of Arunachalem et al. (2001) for hourly observations for North Carolina in 1996. (By the way, Chapter 3 does not indicated which CTM was used.)

Figure AX3-83 tends to mislead the eye. Looking closely at the left-hand tail shows that the model predicts a negligible fraction of daily mean afternoon concentrations below 20 ppbv compared to the data based distribution. In other words, the CTM daily outputs

appear to be shifted to the right. Summary statistics for the two variables would have been helpful. A similar comment applies to Table 3.6 where the discrepancies observed between model and observation occur at the all-important extreme right end of the respective distributions.

Of course, coming back to the Oreskes quotations, we still have no way of ascertaining how well the model predicts the quantities that cannot be measured in estimating the PRB.

10. A major issue with respect to APEX is its accuracy. Is it meant to forecast actual exposures or is it simply meant, like a lot of models are, to have a heuristic role in judging the effects of pollution reductions? If the former, no indication is given about how exactly APEX is to be used in setting standards since no concentration response function is suggested in the Report for use in conjunction with APEX.

11. It is well known that for kriging, a method used in Chapter 3 to map unmeasured concentrations (e.g. see AX3-26), the kriging variance underestimates the uncertainty in spatial prediction. For example, Cressie on p296 of his book on spatial statistics points out that “Brooker finds the kriging variance can be grossly underestimated when the nugget effect is mis-specified”.

The traditional kriging methodology has other shortcomings noted in comments on Chapter 3 of the first AQCD draft. It is ill suited to modeling the spatial – temporal processes of air pollution, relies on the condition of spatial covariance isotropy, and encounters practical problems dealing simultaneously with a vector of pollutants. The latter is a special concern. Even when a single pollutant like ozone is of primary interest, spatial predictors that borrow strength from other pollutants with which it is associated achieve greater predictive accuracy.

The Draft ignores more modern approaches that have been successfully used in modeling and mapping air pollution concentration fields. More discussion and references are given below in the comments below about Section AX3.10.6.2 where other recent approaches are surveyed, albeit incompletely.

COMMENTS ON CHAPTER 3’S ANNEX

All page numbers Y below, meaning AX3-Y, are followed by the appropriate line number. In most cases, the changes are editorial and suggested to improve the clarity and readability of the second draft as it moves toward the final version. Chapter 3 needs to be edited as a result of any changes made in the Annex as a result from these comments.

5-9 replace “countrywide averages” by “countrywide site-wise averages” to avoid the misleading impression that averages across sites have been computed.

5-10 “sites whose data were used in the calculation of background” would be better. Sites cannot calculate!

5-11 “…monitors were operational…”.

5-14 “…concurrence of the local…”

5-25 “and 5% of these site-wise means exceeded 57ppb” would be less confusing. As written, the statement is ambiguous and confusing in light of the 6-2 (where again “countrywide site-wise” should be used).

8-3 “…values indicate the range of O3…”

8-8 “…exhibit relatively coherent spatial patterns of O3 at nonurban…”

9 captions for figures: “…and means (as dots) are shown. Numbers above the boxes are the numbers of observations.”

10-7 Why a “percentile distribution”? Conditional on month, all of the boxplots describe the distribution of measured concentrations.

11 Caption: “Data Pooled Across Monitoring Sites…”. Why is the time period here different from that in the previous table?

13-1 “Such analyses could not be made for…difficulty in finding regions…”

13-3` “Boxplots showing the distributions of …”

13-22 “…pollution because of the large number of…”. Isn’t that really what this is trying to say?

13-23 “…vegetation, use concentration ranges …the range found in the United States.”

13-26 “…in studies of human health and vegetation exposures to O3 appear..” is better.

14-1 “Boxplots in Figures AX3-11a-d depicting the distributions of annual hourly average measured O3 concentrations at four…(RRMS), show that annual mean values of daily 8-hr measured O3 concentration…”

14-8 "…United States represent those of sites…". Why is this point "debatable? It seems obvious.

18 Here is an example of a table that would be simpler and more effective at communicating its information if the redundant "0"s were eliminated by using ppb instead of ppm as the units of measurement. Something should be said about why is part of 1997 missing?

22-9 What does "…first three highest…" mean? Should this be just "…the three highest …"? Again in line 11.

22-23 "…more appropriate values…". More appropriate for what purpose?

26-9 Replace "provided" with "given".

26- A lot of space is devoted to the figures follow. An interpretation should be provided. That is especially true of the confidence intervals. How should the uncertainty they reveal be incorporated into that interpretation?

34 In the hard copy, this figure and its companions are very difficult to read, unlike those in the CD Rom version. For example I could not find any triangles in the figure on this page. I trust that in the published versions of this report things will be made clearer.

It would have been preferable to arrange the symbols in the legend (triangles) etc so that their size corresponded to the level of N100, so for example, the square would have corresponded to the 48-208 category. As well, its customary to arrange these items in ascending rather than descending order of size, 48-208 being at the top rather than bottom, for example, i.e. big is high.

39-2 Here unusually, "average concentrations measured" is used, but this should preferably be "average measured concentrations"

39-3 "Real" should be explained. How did the authors come to that conclusion given the uncertainty indicated by the plots?

40-5 "Many processes contribute…"

40-6 "…downwind of precursor sources."

40-9 "Enhancement" means "To make greater, as in value, beauty, or effectiveness; augment." That is not the intended meaning. "increases" would better here and in the sequel.

40-12 "chosen for analyses to guide risk assessment, to provide…of O3 over different"

40-28 “homogeneity varies with the MSA”

41-2 “(P90) of absolute…”

41-6 “seasons in Table AX3-1, whose length varies across states.”

41-8 “long. However, it typically lasts…”

41-9 “the chosen urban areas”

41-10 “completely different” is nonsensical. I think what is meant here is uncorrelated but in any case, the meaning should be clarified.

41-15 **Reliance on partial MSA’s to obtain reasonable lower estimates. Clarification is needed here. Why is giving a lower estimate of variance desirable over stating the greater variability in a consolidated MSA.**

In the caption “observed” is used. “hourly measured” would be better
That comment pertains to other captions in figures that follow.

49-1 This line is interesting, confirming that although correlations may be high, the pollution series at different sites might be quite different in level. That relates to the general comment above on this topic.

55-13 “50ppb and values as high as this were not found” makes this important point clearly

55-17 “of NO mixing …roadway along with ambient temperatures. So depletions…magnitude, although scavenging of O3…emission controls. Guidance for the placement…” would be better. A paragraph break is needed here for this new topic. Moreover, the last sentence of this paragraph dangles where it is placed.

55-28 This sentence is moved up to where it is better connected.

56-2 “concentrations, consideration must be given to variations…atmosphere.”

56-4 “inner part extends from…”

56-5 “transported material” seems closer to what was intended

56-20 “may resemble those in rural areas more than…. The vertical …vegetation is shown in…”

56-26 “normalized relative to their values at a height of 4 m”

57-1 “strongly stable conditions”. An adverb is needed here to modify the adjective. As written it applies to conditions which is not the intention.

57-4 “1991 (Horvath et al. 2003). The fall off in O3 for this case…”

58-9 “by Mountain…useful information about O3 exposure”

58-12 consistency in the relationship ….”

59-2 “elevation sites (see Table AX-6). Aneja and Li (1992) summarized …1988 (see Table AX3-7).

In 1987…” New paragraph desirable here. Note the sentence that is dropped. Something should be said about the work just referred to. As written these just “hang” there.

59-9 “7-h mean value. In fact, at higher elevations, the 24-h level was larger still (Table AX3-8).” It would be desirable to “set the scene at the outset saying these sites are a decreasing elevations in each case so the reader gets a sense of the big picture behind the detailed discussion.

59-14 The sentence beginning “Both the sum of “doesn’t make sense.

59-15 The elevation of WF4 is not given and yet that of some of the other sites is. For consistency they should all be stated at the outset (see 59-9).

59-16 State what is meant by “sigmoidal values” to communicate these results more effectively.

59-22 As written, a pairwise comparison is being made. How about: “Big Meadows, Dickey Ridge, Sawmill Run and Shendoah..” instead. The text needs to state specifically what “comparisons” are being made here. Between sites? Years?

59-24 The report needs to explain what is meant by a “better resolution”.

59-60 In general, here and the tables that follow, tables should list the source of the data they report. The reason for missing entries should be given. Are these “0”s? If so insert them.

63-7 “requiring” rather “that requires” would make for easier reading. Generally, past and present participial phrases help make writing less verbose.

64- Hard to read the graphs in the hard copy. Why not use “Cumulative” rather than “Integrated” for consistency with the text?

66-3 The sentence beginning “Given the” is hard for the reader to apprehend. Here is a suggested revision: “Even when parts-per-million values at high- and low-elevation sites are equal, the absolute…”

67-10 replace “trivial” by “unimportant”. Then continue: “However the differences between exposure-effects at high- and low-elevation sites may be significant (Lef…). In particular, assuming the sensitivity …target to be identical at low- and high-elevations…”

67-28 The noun “transportation” seems more appropriate than the verb “transport” here.

72- In the caption, a comma is missing: “…whiskers, the minima…”

73-2 Some editing needed in the few sentences beginning here:” …of 1-h O3 averages are broadly similar to 8-h averages. Typically the 8-h daily maximum occurs between 10AM and 6PM, with some deviations from these times.” The last phrase does not really make sense. Deviations from what times?

73-6 “values can start in mid-afternoon and extend into…”

73-16 “plays a major role in determining”

73-19 “The same general timing patterns are found for 1-h daily…concentration as for the daily maximum…”

73-22 “significant numbers of days when...” would be more appropriate.

73-23 “for low values”

76-8 “lower” than what? In fact, “small values” seems to be what was meant.

76-22 “differ” instead of “also vary”

76-28 “elevated weekday O3 concentrates” makes more sense and accords with usage elsewhere in the document

77- Explain here and subsequent plots, what boxes and whiskers mean in the boxplots, as with earlier plots.

79-16 “values for Houston in mid-morning shown in Figure AX3-47, resulted…”

79-25 “precursors and chemical reactions”

79-4 “by the transportation of …”

79-5 “sources, driving…”

81-7 “morning, afternoon and evening”

89- Reminder of the need to insert notes about the meaning of boxes and whiskers, somewhere, perhaps in the individual captions.

92-7 “In contrast, the site” would help the reader grasp what is being said here.

92-8 **What is being said here is not entirely clear. Presumably “more variation” means between sites although at each site there is variation over hours. Can this be quantified in some way? In fact looking at AX3-60, there seem to be two noteworthy sites, one at Whiteface and one at Shenandoah, that latter having more hourly variation than the former in 1987. Is this what is meant? Can this result be replicated using data from another year**?

102-2 “In assessing the effects…on vegetation, it is important…” organizes the content of this sentence better.

102-12 This long sentence needs to subdivided to make its content easier to grasp.

102-17 “less” than what?

102-21 Eliminate the incorrect carriage return here.

103-9 What does “other” mean? There are 3 sites here.

103-12 As written, the ozone is being exposed to the vegetation whereas it should be the other way around.

103-20 “Likewise, the sites…did not always have...exposures.”

103-29 “of” rather than “by”

115-18 “strong association” would be better than “strong correlation”. As noted in the general comments above, “correlation” has the technical meaning of “linear association”. The figures show an interesting strong nonlinear association. Moreover, the uncertainty in that relationship grows as the level of PAN increases.

117- The figure on this page does show a strong correlation between the variables there, not a “Measured correlation” as the caption suggests.

119-26 Here again is a misuse of the notion of correlation. “negatively associated” would be better. But why not “As can…PM2.5, regarded as a function of O3, declines to the left of the inflection point …and increases thereafter.”

120-6 What does “personal basis” mean?

123- The topic of co-occurrence needs a better introduction to explain why it is included in this report. One would have thought the more general issue of the relationships between pollutants more relevant for the purposes of this document. From that perspective, defining co-occurrence narrowly as at the same hour of the day, may conceal some important lag links that relate to the differential rates of formation. Moreover, the low co-occurrence rates did not seem surprising. Why not also include an analysis of co-occurrences within the day (but not necessarily at the very same hour) to allow for the lagged relationships.

126-15 “as previously discussed” where?

126 Note that co-occurrence is taken to be daily here and not above.

138- Why are values missing in this and other tables? What is their source?

151-2 “enhancement” is not the right word as noted earlier. “increase” is what is intended.

158- Notice the typos in the captions on this page and the next.

159- Does background = natural _+ transported stratospheric? If so, that would be worth saying to help interpret the figure on this page.

162-24 “subject to measurement error” would be better.

163-24 “highly correlated” does not mean that the level and variability are the same. In other words, there could well be a bias.

164-4 This paragraph is pretty choppy. I suggest instead: “ In a study discussed later in this chapter, Avol …to measure indoor and outdoor O3 concentrations at 126 homes …widespread use. NEW PARAGRAPH
Ghey eta al.”

165-25 Does this mean the microenvironmental approach used in APEX gives unreliable results? That seems to be what this implies.

166-14 Surely this should be “exposures of large numbers”

167-11 Shouldn't this be something like "latter part of the afternoon"? The day is normally interpreted as extending to midnight.

167-13 This conclusion re co-occurrence disagrees with conclusions earlier in the Annex that are discussed above.

167-29 The etc in this line should be replaced by words that wrap up this list in a more orderly fashion. This paragraph seemed a little discursive since no serious discussion of the various approaches ensues.

168-5 "address" would be preferable to "refer to" given the intended meaning

168-9 Move the sentence starting in line 14 ("It is recognized…studies") which is out of place there to line 9 to get "…model estimates. It is recognized…studies."

168-10 "…provide essential components of a …assessment methodology.

168-13 Drop "but, rather, ambient air estimates." This is redundant. However, if it is kept, at least change it to "ambient concentration estimates."

168-26 Sentence beginning here is too long. You really don't need yet more acronyms in IBM and PBM. These phrases are seldom used in the report. Moreover, the first risks some serious confusion!

168-3 A reference to pCNEM should be given here. It predates APEX, is also built on pNEM concepts, has been assessed against personal monitoring data and has been applied in environmental epidemiology to good effect. That reference to Zidek et al. (2005) appears below.

169-9 "space-time analysis" would be preferable to "geostatistics" since at least traditionally the latter did not admit the analysis of temporal fields. Also "monitor data" should be "monitoring site data"

169-24 "to the maximum feasible extent" would be better.

180- **Section AX3.10.6.2 ignores a substantial body of theoretical work that has been applied in air pollution mapping (Li et al. 1999; Burke et al. 2001 (Duddek et al 1995; Zidek et al. 1998). That work has overcome a lot of the shortcomings associated with the use of classical geostatistics in the context of air pollution. It begins with Le and Zidek (1992) and is extended by them and their co-authors: to incorporate model and in particular spatial covariance uncertainty fully; allows for multivariate responses (Brown et al 1994); to allow data with fixed patterns of missing values (Le et al. 1997; Le et al. 2001; Kibria et al. 2002); to contend with the phenomenon of space-time interaction (Zidek et al. 2002). Moreover, the methodology has been successfully tested (Sun et al. 1998).**

182-16 “To represent uncertainty about it, each parameter is…”

187-12 “AIRS” should be “AQS Database”

204-30 “tract” should be “track”

217-25 The statement here is hard to believe. As written it says the gaseous pollutants are not correlated with one another whereas I think it means PM2.5 was not correlated with any one of them.

COMMENTS ON CHAPTER 3.

3-6-16 What precisely does “defining regions with relatively coherent O3 properties.” Mean?

3-7 See comments about the Annex for changes to the captions in the figure on this and succeeding pages.

3-9-18 “debatable”? See Annex comments.

3-11-10 See comments elsewhere about the term “correlation”

3-12-5 “completely different”? Meaningless. See comments elsewhere.

3-12-14 Explain how was the upper limit of “4” in this line was arrived at.

3-13 What is the time period spanned here and the source of the data?

3-15-12 “collision”? Molecular? Explain.

3-16 All the “action” in this plot is above a rel. concentration of 0.8. Since the horizontal access does not go down to zero anywhere, why not start it at 0.8?

3-33-13 This means “linear spatial interpolation” presumably. If so say so.

3-39-8 A better description than “anti-correlated” is needed as suggested re the Annex.

3-42 Co-currence is too narrowly defined to get at the relationships if any. In fact for PM, the definition shifts to daily rather than hourly co-occerence. Why not shift to daily throughout?

3-50 What part of the “high concentrations” predicted by the methodology used, discussed at the top of this page be ascribed to the model output bias described else in these comments?

3-51 How accurately do the microenvironmental computer models forecast personal exposure? If this is not a source of concern in their application, why is it not?

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Dr. Barbara Zielinska

Comments on the 2nd Draft Ozone AQCD, 2005 Chapter 3

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In my opinion, the revised Chapter 3 of the 2nd Draft Ozone AQMD represents significant improvement over the 1st version. The chapter presents more focused information regarding ozone concentrations in urban and rural areas that are relevant to the health issues discussed in further Chapters. However, there are still some sections of this chapter that would benefit from additional improvements. My few general comments are listed below.

1. There are still some issues how the Annex and the main text of Chapter 3 are integrated together. Some topics are covered much better in the Annex and the chapter summary does not reflect the main points. For example, the section about weekday/weekend differences in ozone concentrations (Section 3.4, page 3-25) is covered much better in the Annex, whereas its summary in the Chapter 3 is too simplistic and not entirely correct. The explanation of these phenomena by the reduced NO emissions on weekends and thus reduced titration of O_3 is not a whole story. As discussed in Heuss et al. (2003) paper cited in this section and in other papers published in the same issue of the Journal of the Air &Waste Management Association, the reduction of NOx in a VOC limited regime may lead to increase in O_3 concentrations, whereas in a NOx limited regime, the reduction of NOx may reduce O_3 levels. These are important implications for ozone precursor control strategies.
2. The section concerning trends in ozone concentrations (Section 3.5) is rather week. There is only a very general statement in this section that the highest concentrations have tended to decrease over the past 15 years, while there has been little change in O_3 concentrations near the center of the distribution. The only explanation offered is the statement that reduced O_3 titration in response to reduction in NOx emissions (page 3-33) may be responsible for this effect. However, ozone is a secondary pollutant and its concentrations depend on its precursors, mostly VOC, NOx and (to a lesser extend) CO levels. Yet, neither the main Chapter 3 nor the Annex provides relevant information regarding trends in the ozone precursors.
3. Section E3 of the Executive Summary states on page E7 - E8 that policy relevant background (PRB) cannot be derived from observations and must be derived from model estimates. However, Section 3.7 discusses uncertainties and limitations of the currently available models and states at the end that the predictions resulting from an ensemble of models should be compared with each other and with observations. The Executive Summary statement seems to be too strong and disconnected from the contents of Chapter 3.
4. The comparison of the GEOS-CHEM model outputs with actual measurements should be included in the main chapter, providing convincing evidence that this global model is suitable for the PRB estimation, especially on the regional and local scale.

5. Although there is an extensive discussion in Chapter 3 (and the Annex) regarding human exposures to ozone, there is only limited presentation and discussion of the use of central monitoring data to estimate exposure. There is no clear conclusion if the central monitoring data is a useful surrogate for use in epidemiological studies and how good the actual personal human exposures compare to the central monitoring data.

Minor editorial comments:

1. Figures 3-2 and 3-3 would be more informative if the data are not shown on the countywide basis, since there are appreciate data variations within counties. Since the 95^{th} percentile (Figure 3.3) is not consistent with the current standard, the 4^{th} highest daily maximum 8-hour concentrations should be plotted for each site in the USEPA AIRS database. The figures would benefit greatly from the use of different colors.
2. Page 3-16 and 3-17, figure captions: ozone concentrations for unstable and unstable conditions?
3. Page 3-25, line 15-16: This is rather peculiar statement. First, ambient O_3 does not have direct sources. Moreover, similarity between diurnal patterns in Houston and Atlanta does not necessary indicate overall similarity in the sources of O_3 precursors.
4. Page 3-25, line 23-24: Awkward sentence.
5. Page 3-34, line 1-2: The full reference to the EPA trend report should be given.
6. Page 3-41, line 1-20. Abbreviations for peroxyacetylnitrate (PAN) and paroxyacylnitrates (PANs) are not used consistently in this paragraph.
7. Page 3-41, line 17: including from Asia?
8. Page 3-42, line 6-7: Awkward sentence. Line 7-9: It is not clear if OH radical concentrations in New York City refer to daytime 12 hr concentration range or 24-hr range. In any case, 1.6×10^6 molecule/cm^3 is an average 12-hr OH radical concentrations, so 1.8×10^6 is not really high.
9. Page 3-62, line 15-19: although PAN is formed from the reaction of OH or NO_3 radicals with acetaldehyde, followed by O_2 and NO_2 reactions, the abundance of OH and especially NO_3 radicals in an indoor environment is expected to be rather low, so this reaction is not a significant source of indoor PAN.
10. Page3-63-65, Table 3-4. Some ozone concentrations in this Table are suspiciously low. For example indoor/outdoor concentrations listed for Munich, Germany, are below 1 ppb. This is below the detection limit of most ozone monitors.
11. Page 3-67, line 1-25 and Annex, pages AX3-209 – 213 (Ozone Removal through Chemical Processes). Although it is important to emphasize the possibility of ozone reactions in indoor environments and formation of potentially more toxic products, the section should put these processes in perspective. The long list of potential products of O_3 reactions with terpenes and alkenes is not very informative and the section lacks the bottom line regarding the actual products (and their concentrations) observed in indoor environments. What is the reason of citing some works that used concentrations of reactants (i.e. O_3, terpenes, NO_2, etc.) many times higher than typical indoors conditions (Annex, page AX213, lines 1-8)? What does “various nitrogen compounds... and other compounds” mean (page 3-67, line 13-15)? Page AX3-212, line 25: what does (as toluene) mean?

12. Page 3-72, line 15: “peroxyacyl radicals”.
13. Page 3-74, line 22-30: see comment 11
14. Page 3-75, line 3-8: I think that Ogawa passive O_3 monitors have been shown to be quite reliable. Also, strong correlations between O_3 measured by stationary monitors and personal monitors don’t mean that the measured values are similar – one could be consistently lower than the other, but they still could be correlated.

NOTICE

This report has been written as part of the activities of the U.S. Environmental Protection Agency's (EPA) Clean Air Scientific Advisory Committee (CASAC), a Federal advisory committee administratively located under the EPA Science Advisory Board (SAB) Staff Office that is chartered to provide extramural scientific information and advice to the Administrator and other officials of the EPA. The CASAC is structured to provide balanced, expert assessment of scientific matters related to issue 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 in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use. CASAC reports are posted on the SAB Web site at: http://www.epa.gov/sab.